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GIANT CELL PNEUMONIA WITH INCLUSIONS

A LESION COMMON TO HECHT'S DISEASE, DISTEMPER AND MEASLES *

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Giant cell pneumonia was first described by Hecht [1] in 1910. Clinically, there is little to distinguish the condition from other types of subacute or chronic pneumonia in infants. Measles, tuberculosis, or syphilis may be associated with it, but it often occurs in an apparently uncomplicated form. Although Hecht found the condition in 27 instances among 162 cases of pneumonia in infants and young children, only a few cases have been reported since 1910.

The diagnosis of giant cell pneumonia is made on the basis of the histological picture. The lesion is an interstitial pneumonitis, the most important diagnostic feature of which is the formation of large multinucleated cells by proliferation and fusion of the cells which line the alveoli, alveolar ducts, and bronchioles. As has been pointed out by Moore and Gross,[2] giant cells of several different types may occur in the lungs of infants under a variety of conditions. Many observers, however, including Chown,[3] have felt that the picture of Hecht's giant cell pneumonia,[1] in its fully developed form, represents a distinct pathological entity. Chown believed that the cause of the condition might be vitamin A deficiency. This etiological theory was soundly based on histological evidence, and will be discussed later.

In examining the sections of a typical case of giant cell pneumonia (previously unreported) numerous and prominent cytoplasmic inclusions were noted in giant cells, and also in alveolar and bronchial lining cells. This led us to examine sections of 4 other cases of giant cell pneumonia. Three of these had been reported previously (Chown,[3] Masson and Paré,[4] Karsner and Meyers [5]) while the fourth (unpublished) was made available by Dr. Masson. In all 4 of these cases, many cytoplasmic inclusions, similar to those seen in the first case, were present, and intranuclear inclusions were also found in large numbers.

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The striking morphological resemblance of these cytoplasmic and nuclear inclusions to those associated with distemper in animals led us to make detailed comparative studies of the two conditions. The occurrence of giant cells in lymphoid tissue in prodromal measles suggested the inclusion of tissue from fatal measles in our study.

Observations in Giant Cell Pneumonia

Case 1

(Previously unreported.) B. C., a Negro female infant, was born spontaneously at the Homer G. Phillips Hospital after 33 weeks of gestation. Crying was spontaneous; respiration and color were good. The birth weight was 2,370 gm. The mother was described as well nourished and in good health. She had attended a prenatal clinic and was on a supposedly adequate diet. She had one child living and well, 18 months of age. The infant was placed on the breast after the first 8 hours and fed six times daily for the next 3 days. Diarrhea developed on the 4th day. The infant was placed on a formula of condensed milk and the diarrhea ceased, but the weight loss continued. On the 9th day the infant became markedly cyanotic with rapid respirations. Examination at this time failed to reveal any pulmonary findings. X-ray examination of the chest was negative; Kahn test of the blood was negative; hemoglobin, 90 per cent; erythrocytes, 5,200,000; white blood cells, 7,400; temperature, 98.8° F. (rectal). Medication consisted of 25 cc. of Hartman's solution, subcutaneously, and 15 cc. of whole blood. Following this, clinical improvement was noted. Respirations became slower and less labored. The color became normal; temperature remained normal. On the 14th hospital day the infant again became cyanotic and dyspneic, and expired after 3½ hours.

Necropsy was performed 6 hours post-mortem. Subcutaneous and perivisceral fat was scanty in amount. There was evidence of dehydration. Exclusive of the lungs, the findings were as follows: Heart, spleen, stomach and intestines, adrenals, thymus, brain, normal; liver and kidneys, cloudy swelling. The lungs grossly showed glistening, moist pleural surfaces. They were dark red at the bases, tending to fade to a bright red at the apices. They were somewhat collapsed, rather firm in consistency and cut with increased resistance. The cut surface was moist and of a deeply congested homogeneous appearance. The grayish nodules characteristic of consolidation were noticeably absent. The bronchi contained a thick, reddish gray, viscid material.

Microscopical examination of the lungs (hematoxylin and eosin stain) showed intense congestion of the alveolar capillaries, and infiltration of the alveolar walls by many mononuclear cells, together with rare neutrophils. Many alveoli were collapsed, but those which were patent contained a serofibrinous exudate in which a few large, vacuolated mononuclear cells were present. The bronchioles contained a fibrinous or mucoid exudate, with desquamated epithelial cells and occasionally with moderate numbers of neutrophils.

On low-power examination, 10 to 15 large multinucleated cells were present in nearly every field (Fig. 1). On high-power study, these

giant cells were seen to be derived from the lining cells of the alveoli, alveolar ducts and bronchioles. The alveolar lining cells, when not forming giant cells, commonly showed cuboidal metaplasia and were often in mitosis.

Cytoplasmic inclusions were present in about one-half of the giant cells, in the epithelium of most of the bronchioles, and in many of the hypertrophied alveolar lining cells. A giant cell showing 15 to 20 nuclei often showed as many as 8 to 10 inclusions, and occasionally there were more inclusions than nuclei. The inclusions varied from light pink to reddish purple, depending on the relative intensity of the staining with hematoxylin and eosin. In the bronchioles, they were most often found in those areas where the epithelium projected into the lumen in the form of a multinucleated syncytial bud (Fig. 2). In the bronchial epithelium, the inclusions ranged from 2 to 10 μ in greatest dimension, and were most often roughly spherical or ovoid. In the giant cells, they ranged up to 25 μ in greatest dimension, and showed greater morphological variation (Fig. 3). Frequently small vacuoles could be seen in the substance of the inclusions, and many of the medium-sized spherical forms resembled Negri bodies rather closely. The inclusions were frequently paranuclear in location, and occasionally the adjacent nuclei were indented.

Prolonged study showed no definite nuclear inclusions. No inclusions of any type were found in sections of liver, pancreas, or kidney (pelvic epithelium not included). A few cytoplasmic inclusions of moderate size were found in reticulo-endothelial cells in the spleen.

Case 2

(Previously reported by Masson and Paré.[4]) A 9-month-old infant was admitted to the hospital with a cough of 1 month's duration, and dyspnea. A rash occurred at the beginning of the illness. The clinical diagnosis was pulmonary tuberculosis and tuberculous meningitis. Death occurred about 4 weeks after admission to the hospital.

Autopsy showed miliary tuberculosis, rickets, caseous tuberculous lymphadenitis, and bronchopneumonia with bronchiectasis.

Microscopical examination of the lungs stained with hematoxylin and eosin and by the Giemsa method showed many small tubercles with caseous centers and giant cells of the type commonly seen in tuberculosis. In addition to this picture, however, syncytial multinucleated cells arising from alveolar and bronchiolar lining cells were numerous, and in spite of the presence of the lesions of tuberculosis, the diagnosis of Hecht's giant cell pneumonia [1] could be made with confidence. The giant cells of the "tuberculous" type could be distinguished, in most instances, from those characteristic of giant cell

pneumonia by the tendency of the latter to be attached to alveolar and bronchiolar walls (or, if lying free, by the presence of elongated strands of cytoplasm) and by the commonly central location of their nuclei. In many of the giant cells of the latter type, cytoplasmic inclusions identical with those described in case 1 were present in large numbers.

Nuclear inclusions were present also in large numbers in the nuclei of giant cells, alveolar lining cells and bronchiolar epithelial cells (Fig. 4). These nuclear inclusions most commonly filled only one-fourth to one-third of the nucleus. They were homogeneous, eosinophilic, and rounded or oval. The nuclear inclusions were often stained less intensely than the cytoplasmic, as though the nuclear membrane had acted as a barrier to the penetration of the stain. By overstaining with eosin, the nuclear inclusions could often be brought out more clearly, at the expense of definition of the cytoplasmic bodies. In cells where nucleoli were present, they were readily differentiated from the latter structures by differences in size and staining characteristics. The inclusions were nearly always surrounded by a wide zone of clearing in the nuclear chromatin. Many of the affected nuclei were enlarged, and occasionally a suggestion of margination of the nuclear chromatin was seen. The latter feature, however, was inconspicuous.

Case 3

(Previously unpublished. Made available through the courtesy of Dr. Masson.) The patient was a girl, 2½ years old, who had had subacute bronchopneumonia of about 6 weeks' duration, with suppurative pneumococcal pleuritis.

Microscopical examination of the lungs showed interstitial pneumonitis. In many areas the alveolar walls were crowded with mononuclear cells, while the alveoli contained serous fluid with only a few mononuclear cells. In other areas, alveoli and bronchioles contained a purulent exudate, probably the result of secondary infection. There was a striking tendency for the alveolar lining cells to undergo cuboidal metaplasia. Giant cells of the type described in cases 1 and 2 were present, but in smaller numbers than in the other 4 cases included in this series. In several areas, only one or two giant cells were present in ten low-power fields. The giant cells showed a tendency to be most numerous in the regions adjacent to interlobular septa.

In alveolar lining cells, bronchial epithelium, and giant cells (Fig. 5), cytoplasmic and nuclear inclusions apparently identical with those described in cases 1 and 2 were present in large numbers. They were eosinophilic when stained with either hematoxylin and eosin or Giemsa's stain.

Case 4

(Previously reported by Chown.[3]) The patient was an infant with a previous history of congenital syphilis, which was apparently cured by treatment. At the age of 16 months, spreading bronchopneumonia developed, and this condition terminated fatally 26 days later.

At autopsy the main gross finding was bilateral bronchopneumonia.

Microscopical examination of the lungs showed giant cells fully as numerous as in case 1. Histologically, the inflammatory cell reaction was largely mononuclear in some areas, while in other areas many neutrophils were present. It should be pointed out that in certain blocks of lung tissue, giant cells were present only in very small numbers. Nuclear and cytoplasmic inclusions identical with those described in cases 1, 2 and 3 were present in alveolar lining cells, bronchial epithelium and giant cells. Nuclear inclusions were found less uniformly throughout the sections than in cases 2 and 3, but were numerous in localized areas. Cytoplasmic inclusions were more numerous in this case than in any of the others.

Case 5

(Previously reported by Karsner and Meyers.[5]) An 18-month-old infant was admitted to the hospital with severe rickets and diffuse bronchopneumonia. An illness which was probably bronchopneumonia had occurred 1 month before entry, but the patient apparently had recovered. Death occurred after an illness of 2 weeks.

Autopsy showed patchy bronchopneumonia. Cultures from the lung tissue showed staphylococci.

Microscopical examination of the lungs showed numerous giant cells of the type described in the other cases. In most areas, the originally mononuclear reaction was obscured by a reaction of the purulent type. The giant cells, bronchiolar epithelium and alveolar lining cells contained large numbers of cytoplasmic inclusions like those described in the other cases. Nuclear inclusions were present in moderate numbers. It is of interest to note that in a section stained with eosin and methylene blue the inclusions were brightly eosinophilic and prominent, while in a section stained by hematoxylin and eosin the inclusions were made out with difficulty. (Neither of these sections had been restained since 1911.)

No inclusions were found in sections of lymph node, spleen, thymus, or kidney (pelvic mucosa not included). In the single section of liver available for study, five fairly characteristic cytoplasmic inclusions were found in bile duct epithelium. The section was somewhat faded, and it was not possible to be certain that these inclusions were authentic. The question of the presence of inclusions in organs other than the lung in giant cell pneumonia requires further study.

Observations in Distemper

For the histological study of distemper, sections from 63 minks, 22 ferrets and 12 foxes were available. These sections were prepared in 1938, in the course of a study of epidemics of distemper in minks and foxes. The histological picture of distemper virus pneumonia as seen in this material was reported briefly by one of us in 1940.[6] In that report multinucleated cells containing the characteristic inclusions of distemper were described in the lungs, but the possible relationship of the lesion to giant cell pneumonia was not considered at that time. In the present paper, this pulmonary lesion will be described in greater detail.

In minks, the lungs were believed to show the picture of uncomplicated virus infection. The lungs from a few of the minks showed only intense congestion, with cytoplasmic inclusions in the bronchiolar epithelium. These were probably cases in which early death occurred from overwhelming infection. In the great majority of instances, however, patchy areas of consolidation, 1 to 5 mm. in diameter, were found, and in several instances there was almost uniform consolidation of one or more lobes. On microscopical examination, the alveolar walls in the consolidated areas were greatly thickened, and contained large numbers of macrophages and plasma cells. The alveolar lining cells were hypertrophied, and often in mitosis. Large multinucleated cells, obviously derived from the alveolar lining cells by proliferation and fusion, were found in variable numbers in different cases. The alveoli often contained a few mononuclear cells, some of which were vacuolated and appeared to be macrophages, while others appeared to be desquamated alveolar lining cells. Neutrophils were inconspicuous. Giant cells often appeared to lie free in the alveoli, but careful study of several sections mounted on the same slide suggested that many of these were still attached to the alveolar walls, and were in reality parts of an extensive irregular syncytium. The bronchiolar epithelium also showed marked metaplasia, with occasional giant cell formation.

In many sections of the lungs of minks, giant cells were prominent in only one or two small areas, particularly in a subpleural position, or adjacent to connective tissue septa. In several, however, giant cells were numerous throughout the slide. In these cases, the resemblance to Hecht's giant cell pneumonia[1] appeared complete in all details (Fig. 6).

In sections of the lungs of ferrets and foxes, a purulent exudate in the alveoli was the rule. This is believed to be the result of secondary bacterial infection.

Metaplasia and proliferation of bronchial and alveolar lining cells

was nearly always obvious, however, and giant cells were present in many cases. In one ferret and in at least one fox, giant cells were sufficiently numerous to suggest "giant cell pneumonia."

Inclusion Bodies

Inclusions characteristic of distemper were found in the epithelium of the bronchioles (Fig. 7) and also in alveolar lining cells and in giant cells derived from cells of these two types (Figs. 8 and 9). In all animals, cytoplasmic inclusions were numerous; nuclear inclusions were more variable, being numerous in the majority of animals and demonstrable in nearly every animal. In 2 minks, however, no nuclear inclusions could be found.

The inclusions in this distemper material were not described in detail in the previous report [6] because it was felt that they had been described adequately by other workers.[7,8] The most detailed descriptions and the best illustrations of distemper inclusions in the literature probably are to be found in a paper by Green and Evans.[8]

Observations in Fatal Measles

Through the courtesy of Dr. James Denton, sections from 6 fatal cases of measles, which occurred in Panama in 1923 in an epidemic with high mortality, were made available.

Pulmonary Lesions. In 3 of these 6 cases, the lungs showed purulent bronchitis and bronchopneumonia, the appearance of which was in no way suggestive of giant cell pneumonia or of any other type of virus pneumonia. In 2 cases, giant cells with many typical cytoplasmic and nuclear inclusions were present, giving a picture indistinguishable from that of Hecht's giant cell pneumonia or from that of distemper virus pneumonia in animals. In the sixth case, the sections from which were faded, a few giant cells were seen, and a few intracytoplasmic bodies were present which were strongly suggestive of the above described type of inclusion. It is of interest to note that Denton,[8a] in his original description of this material from cases of measles in 1925, stressed the presence of giant cells in the lungs.

Lesions in Other Organs. No giant cells or inclusions were found in sections of heart, spleen, liver, kidney, pancreas, small intestine, or lymph nodes.

Discussion

Inclusions

The distinctive features of the cytological picture associated with distemper infection may be summarized as follows:

1. Occurrence of both nuclear and cytoplasmic inclusions (a rare finding in other virus infections).

2. Presence of inclusions in huge numbers; often 6 or 8 inclusions in a single cell, and 25 or more inclusions in a section of a multinucleated cell.

3. Location of inclusions in alveolar and bronchiolar lining cells, bladder epithelium, and less constantly in bile and pancreatic duct epithelium, skin, and adrenal cortical cells.

4. Cytoplasmic inclusions homogeneous or vacuolated, somewhat resembling Negri bodies; nuclear inclusions rarely if ever vacuolated.

5. Extraordinary range in size of cytoplasmic inclusions (1 to 30 μ) while nuclear inclusions range only from about 1 to 5 μ, rarely filling more than one-third of the nucleus.

6. Marked variation in shape of cytoplasmic inclusions: usually rounded or ovoid, but may be sausage-shaped, vermiform, or irregularly polygonal.

7. Nuclear inclusions more constant in shape, round or ovoid; nearly always occurring singly.

8. Color of inclusions with hematoxylin and eosin stain ranges from light pink to purple, depending on relative intensity of staining with each.

9. Cytoplasmic inclusions often paranuclear, and may cause indentation of adjacent nuclei.

The cytological picture of distemper, when all of its details are considered, is unique and quite unlike that of any other known virus infection. It has generally been regarded as having diagnostic significance.[6,8] If one compares the nuclear and cytoplasmic inclusions seen in the lungs of cases of giant cell pneumonia of infants (Figs. 2, 3, 4 and 5) with those seen in lungs of animals with distemper (Figs. 7, 8 and 9) and with the picture of distemper as illustrated by Green and Evans,[8] and other workers, the apparent cytological identity of the two conditions is evident. On this basis alone, one might be justified in concluding that we are dealing with closely related, if not with identical viruses.

The apparent absence of nuclear inclusions in case 1 is paralleled by the occasional failure to find nuclear inclusions in distemper (observations above and also those by Green and Evans[8]). In the other 4 cases studied, characteristic nuclear as well as cytoplasmic inclusions were present. The characteristic pleomorphism of the cytoplasmic inclusions in case 1, and the histological identity of the pulmonary lesion to that seen in the other 4 cases suggest that all 5 cases are

etiologically identical, and that the absence of demonstrable nuclear inclusions in case 1 is purely fortuitous.

Histological Observations

The essential histological identity of the pulmonary lesions in several cases of pneumonitis of distemper in minks (Fig. 6), foxes, and ferrets with those in giant cell pneumonia (Fig. 1) lends additional support to the view that the two conditions may be closely related etiologically. In the lungs of the animals with distemper, the characteristic giant cells were present in sufficient number to suggest giant cell pneumonia in only a small percentage of the cases. This suggests that the diagnosis of giant cell pneumonia in infants may be missed in many cases because the giant cells are not present in sufficient numbers. It has been pointed out that giant cells were not numerous in case 3, and that in certain blocks of lung tissue in case 4 they were present only in small numbers, while in other blocks they were extremely numerous. In subsequent studies, particular attention should be paid to lungs of infants containing even occasional giant cells, in the absence of a good reason for their presence.

Hypertrophy and cuboidal metaplasia of alveolar lining cells, without giant cell formation, occur in lungs under a wide variety of conditions, including several varieties of virus pneumonia and toxoplasmosis.

Nature of the Virus in Giant Cell Pneumonia

That giant cell pneumonia is a virus disease seems clear beyond a reasonable doubt on the basis of the cytological changes described above. Either the cytoplasmic or the nuclear inclusions alone would strongly support such a conclusion. The occurrence of the two types of inclusions together, often in the same cell, is believed to be conclusive evidence of virus activity.

It has already been pointed out that the inclusions present in the cases of giant cell pneumonia are identical with those of distemper, and that giant cell pneumonia occurs in distemper. Identical nuclear inclusions do not necessarily imply identical or even closely related viruses, and the same may be said of identical cytoplasmic inclusions. When both nuclear and cytoplasmic inclusions are identical, however, and when this identity includes a wide range of morphological variation, it is difficult to believe that the viruses involved are not closely similar.

Strain variations in distemper of such a degree that cross-immunity does not obtain have been described by Slanetz and Smetana.[9] Their

two viruses, although morphologically identical and producing essentially identical clinical pictures in ferrets, were immunologically distinct.

Assuming that the evidence presented here for a close relationship between the virus of giant cell pneumonia and distemper is valid, the exact relationship between the two viruses can be determined only when the former virus is finally isolated in an experimental animal susceptible to distemper.

An important factor in deciding the question of the identity of two viruses—perhaps even more important than the character of the inclusions—is their distribution and their preference for growth in cells of certain types. The cytoplasmic inclusions of canine distemper, for example, may greatly resemble the Negri bodies of rabies. The occurrence of the latter exclusively in the ganglion cells of the brain, however (as well as the absence of intranuclear inclusions), serves to differentiate them sharply.

It has been shown that in the lung the inclusions of giant cell pneumonia are found in cells of the same types as in distemper. Unfortunately, material has not been available for a satisfactory topographical study of inclusions in other organs. Bladder tissue, the most common location for distemper inclusions outside of the lungs, was not available in any case. Inclusions were found in the reticulo-endothelial cells in the spleen in case 1, as they are in distemper. In case 5 they were probably present in bile duct epithelium, where they are often present in distemper. Further study is necessary before it can be concluded that there are no differences in organ distribution and cytotropism in the two conditions, but as far as our observations go, no differences have been found that are significant.

The occurrence in some cases of measles of giant cell pneumonia, identical both histologically and cytologically with Hecht's disease and pneumonia of distemper, raises the question of the interrelationship of these three conditions. It is possible, or perhaps probable, that Hecht's disease may be caused by the action of the measles virus in certain persons who, because of low resistance or for some other reason, do not develop the characteristic rash, Koplik spots, etc. If this is true, Hecht's disease should be regarded as identical with pneumonia produced by the virus of measles. On the other hand, certain considerations, particularly the chronicity of Hecht's disease and the usual absence of giant cell pneumonia or inclusions in fatal measles, suggest the possibility that two distinct viruses may be involved, only one of which causes a distemper-like morphological picture. Morphological

studies of the tissues of monkeys infected from human cases of measles should help to clarify the situation.

Distemper in Man

Evidence for the occurrence of distemper in man has not been reported as far as we have been able to learn, although there has been speculation concerning this possibility. The title of a paper by Taskin [10] suggests that canine distemper virus may produce inapparent infection in man. We have not been able to obtain the journal in which this paper was published.

The apparent enhancement of immunity to influenza by the distemper virus reported by Horsfall and Lennette [11] and the possible sparing effect on poliomyelitis noted by Dalldorf and Douglass [12] suggest a relationship between the distemper virus and other virus diseases of man. Eichorn and Pyle [13] found cross-immunity between distemper and influenza in ferrets, but this observation apparently has not been constant, since it has not subsequently been reported.

Relation to Vitamin A Deficiency

Chown [3] believed that the pathological changes in the lungs in giant cell pneumonia were a manifestation of vitamin A deficiency. This theory is of interest because of the fact that many of the clinical features of distemper resemble those of vitamin A deficiency. In ferrets and minks, hyperkeratinization of the skin of the paws and the occurrence of pustular lesions in the hair follicles, particularly around the nose and mouth, are definitely suggestive of vitamin A deficiency. In the bladders of ferrets, minks and foxes we have noted marked thickening and desquamation of the mucosal epithelium. This thickening is often most marked in the regions where inclusions are most numerous. Barondes [14] believed that some of the symptoms of distemper in dogs were suggestive of vitamin A deficiency. The possibility is suggested that the presence of the distemper virus in cells, with the consequent profound changes in cellular metabolism, may render the cells unable to utilize vitamin A. On the other hand, the metabolic disturbance caused by the virus in the cells (and manifested morphologically by the presence of the inclusions) may, by some other mechanism, bring about changes resembling those of vitamin A deficiency. This aspect of the problem is under investigation.

Epidemiological Possibilities

Distemper is primarily a disease of young animals. That the predilection for the young is not entirely explained on the basis of previ-

ous immunization of adults by subinfectious doses is indicated by the fact that in outbreaks of distemper on mink ranches, previously uninfected, the morbidity and mortality is much higher in young than in adult minks.[6]

Direct transmission of distemper from dogs to infants is a possibility which perhaps should be considered. In case 1 reported here, contact with animals was not a possibility, since the infant did not leave the hospital. The possibility that distemper infection may be latent in man should be investigated. With toxoplasmosis it is well known that infants may acquire fatal infection while *in utero* and in the absence of clinical manifestations of the disease in the mothers. Given the condition of latent infection in infants, other diseases such as measles, tuberculosis and syphilis might lower resistance and allow a distemper-like virus to produce pathological changes.

Relation to Other Virus Pneumonias of Infants

The inclusions described here are totally unlike those of "inclusion disease," described in lungs by Farber and Wolbach,[15] and others. In this condition, an instance of which was observed here recently, large cells are seen in the pulmonary alveoli, but these cells are rarely multinucleated. The nuclear inclusions are large and granular, filling and distending the nuclei.

The virus pneumonia of infants described by Goodpasture, Auerbach, Swanson and Cotter [16] does not show giant cells. Nuclear inclusions are granular and often fill the nuclei. Cytoplasmic inclusions do not occur. These features seem to distinguish this condition from giant cell pneumonia.

The virus pneumonia in infants described by Adams [17] is apparently unassociated with giant cell formation. Cytoplasmic inclusions occur in this condition. Certain of these inclusions resemble those seen in giant cell pneumonia (on the basis of published descriptions and illustrations and of our own observations on one section which we have studied). The cytoplasmic inclusions, however, are relatively small and relatively constant in size and shape, in contrast to the pleomorphism of the inclusions seen in giant cell pneumonia and in distemper. The absence of discoverable nuclear inclusions in carefully studied material from many cases also suggests that this is probably a different type of virus pneumonitis.

Two reports are found in the literature of pneumonia in measles associated with giant cells and cytoplasmic inclusions, but without nuclear inclusions. The case reported by Semsroth [18] was believed to be one of prodromal measles, although the clinical description was not

clearly that of measles. The case reported by Masugi and Minami[19] apparently was one of measles, but it is not clear whether giant cell pneumonia in these 2 cases was a manifestation of the activity of the virus of measles or of some other virus.

The occurrence of giant cells in lymphoid tissue early in the course of measles[20] is a well recognized pathological lesion of considerable interest. In the course of our studies, the possibility occurred to us that these giant cells and the giant cell pneumonia might be a manifestation of the action of the same virus. The only material available to us was a section of appendix from a case of prodromal measles. Careful study of the giant cells in the lymphoid tissue of this appendix revealed no cytoplasmic inclusions, and no definite nuclear inclusions, although an occasional suggestion of the presence of a nuclear inclusion was noted.

In distemper and in giant cell pneumonia, giant cells are absent from lymphoid tissue. Green and Evans,[8] however, have described giant cells with inclusions characteristic for distemper arising from cells of the adrenal medulla and from liver cells.

The occurrence of giant cells in tissues from patients with measles requires further study from the point of view of distribution and the presence of inclusion bodies. At present it is not clear whether they indicate the action of the measles virus or of some concomitant virus, such as, for example, that of giant cell pneumonia.

Summary and Conclusions

In a study of lung tissue from 5 cases of Hecht's giant cell pneumonia in infants, cytoplasmic and nuclear inclusions were found in 4 cases, while in a fifth case cytoplasmic inclusions alone were observed. The inclusions are found in bronchiolar epithelium, in alveolar lining cells and in giant cells arising from the latter two types of cells. Both cytoplasmic and nuclear inclusions are of the type associated with virus activity. The cytoplasmic inclusions are multiple, often vacuolated, and show marked variation in size and shape, while the nuclear inclusions are usually single, rarely filling more than one-third of the nucleus, and relatively constant in size and shape.

The cytological picture presented by this combination of cytoplasmic and nuclear inclusions is identical with that seen in distemper in dogs and other lower animals, and is quite unlike that seen in any other known type of virus infection. It is generally believed to be diagnostic of distemper in animals.

The virus of distemper in minks, ferrets and foxes causes an interstitial pneumonia in which giant cell formation from alveolar and

bronchiolar lining cells is a prominent feature. In several instances, giant cells of this type were found in large numbers, and the histological picture of giant cell pneumonia appeared to be duplicated in every detail. As in the cases of human giant cell pneumonia, the inclusions were located in bronchiolar and alveolar lining cells, and in the giant cells.

In sections from 2 of 6 fatal cases of clinically typical measles made available by Dr. Denton, an identical picture of giant cell pneumonia with nuclear and cytoplasmic inclusions was found. Possible interpretations of our observations are: (1) that giant cell pneumonia is a lesion caused by the measles virus, which may occur with or without the usual clinical manifestations of measles; and (2) that giant cell pneumonia is caused by another virus which may act independently or in association with the measles virus. In either case, the histological and cytological identity of the pulmonary lesions of giant cell pneumonia with those of canine distemper suggests that there is a close biological relationship between the two diseases.

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[*Illustrations follow*]

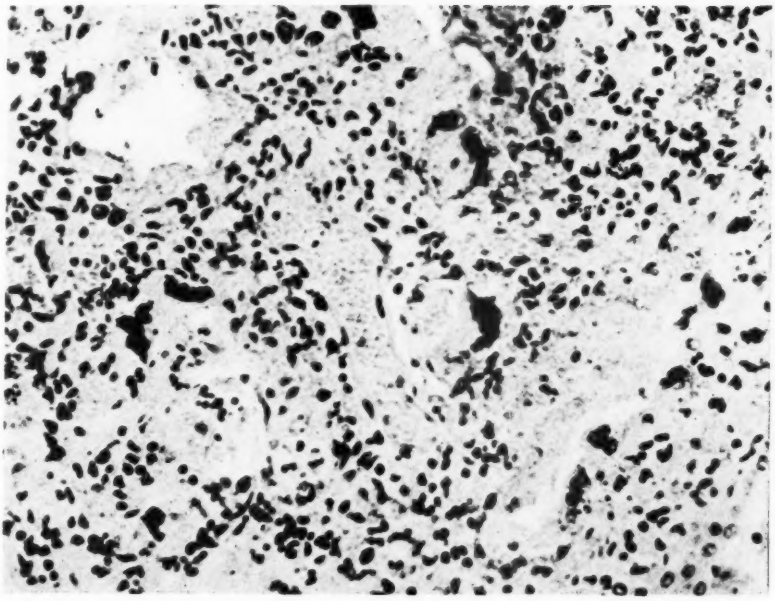
DESCRIPTION OF PLATES

PLATE 1

FIG. 1. Giant cell pneumonia in an infant (case 1), illustrating the distribution and appearance of the giant cells, most of which are derived from alveolar lining cells. Hematoxylin and eosin stain. × 280.

FIG. 2. Case 1. Syncytial multinucleated cell arising from the epithelium of a bronchus, and containing two inclusion bodies of medium size. (Arrows point to the inclusion bodies.) Hematoxylin and eosin stain. × 1000.

1



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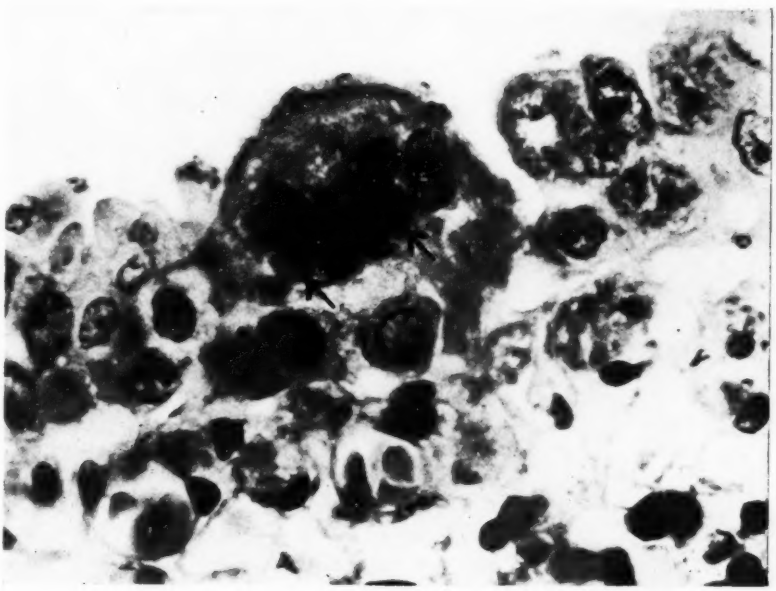


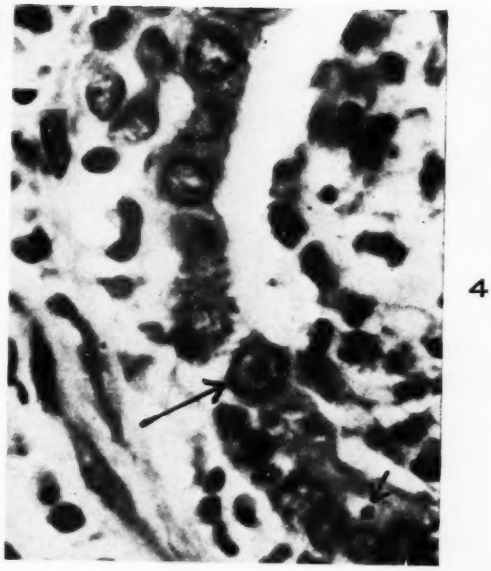
Pinkerton, Smiley and Anderson Giant Cells in Pneumonitis

PLATE 2

FIG. 3. Case 1. Giant cell in an alveolus, containing a large, irregularly shaped inclusion, and two smaller inclusions, one of which is in a paranuclear position. Hematoxylin and eosin stain. × 1000.

FIG. 4. Case 2. A typical nuclear inclusion is seen in an epithelial cell lining a small bronchiole. A small cytoplasmic inclusion is also shown. Hematoxylin and eosin stain. × 1000.

FIG. 5. Case 3. Multinucleated cells arising from alveolar epithelium in which two nuclear inclusions and seven cytoplasmic inclusions are shown. Other cytoplasmic and nuclear inclusions are present but not in focus. (Long arrows point to nuclei with inclusions and short arrows to cytoplasmic inclusions.) Hematoxylin and eosin stain. × 1000.



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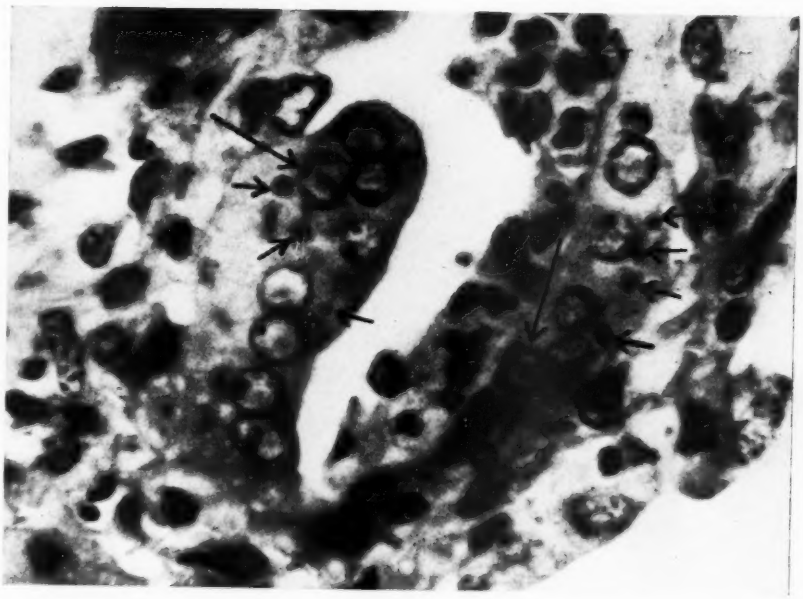


5

Pinkerton, Smiley and Anderson

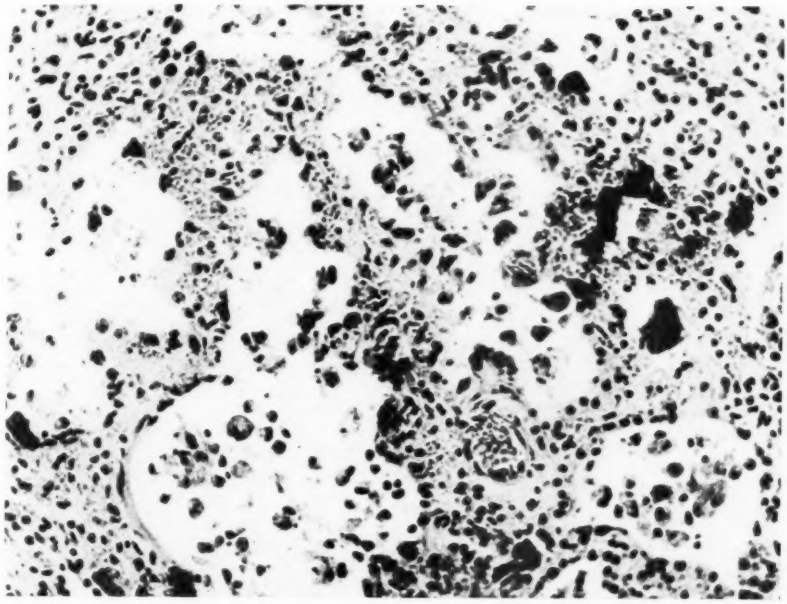
Giant Cells in Pneumonitis

PLATE 3

FIG. 6. Distemper pneumonitis in a mink showing many giant cells arising from alveolar lining cells. This picture is similar to that seen in giant cell pneumonia (Fig. 1). Hematoxylin and eosin stain. × 280.

FIG. 7. Bronchial epithelium from the lung of a mink. Numerous deeply stained cytoplasmic inclusions are shown, with marked variation in size. Hematoxylin and eosin stain. × 1000.

6



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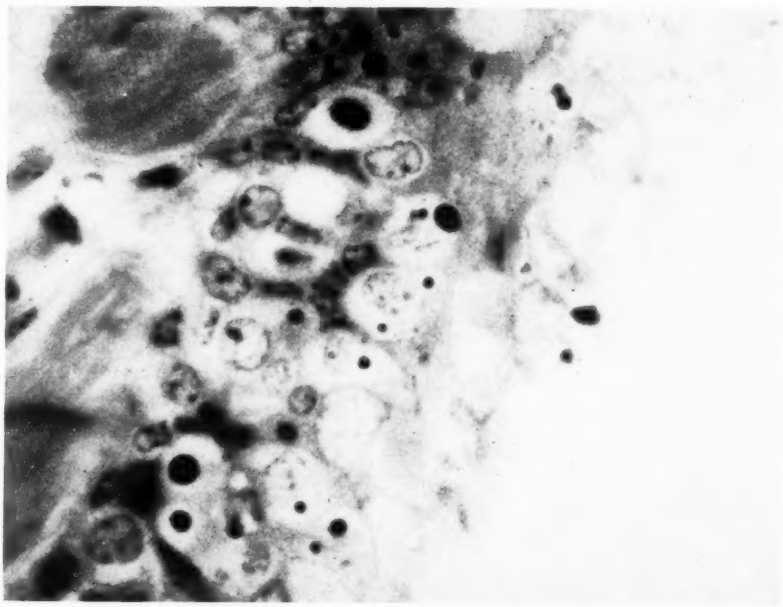


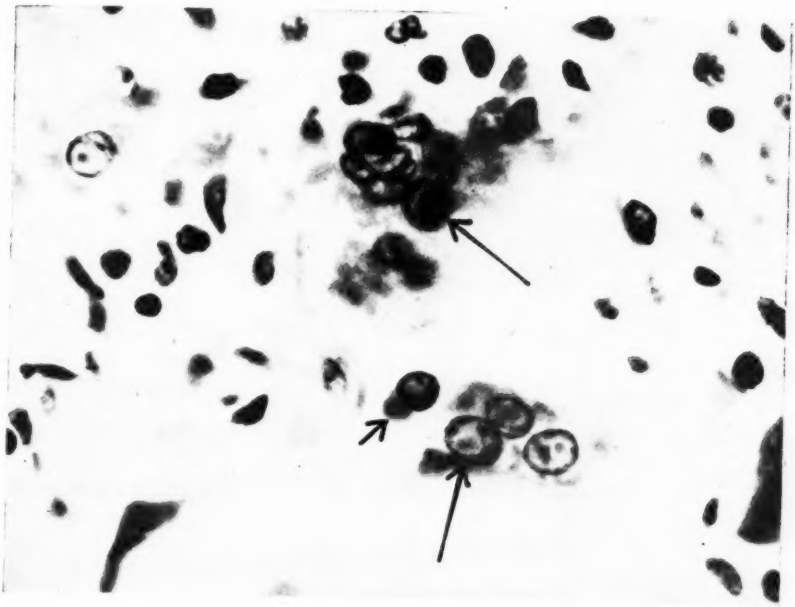
Pinkerton, Smiley and Anderson Giant Cells in Pneumonitis

PLATE 4

FIG. 8. Distemper pneumonitis in a mink. Two nuclear inclusions and one paranuclear cytoplasmic inclusion are seen in giant cells lining an alveolus. Other cytoplasmic inclusions are present, but not in focus. This picture, which is typical of distemper, is to be compared with Figures 4 and 5, showing a similar picture in the lung of an infant. Hematoxylin and eosin stain. × 1000.

FIG. 9. Distemper pneumonitis in a mink. Two giant cells arising from alveolar lining cells are shown. One of the giant cells contains three cytoplasmic inclusions. This picture is similar to that shown from the lung of an infant in Figure 3. Hematoxylin and eosin stain. × 1000.

8



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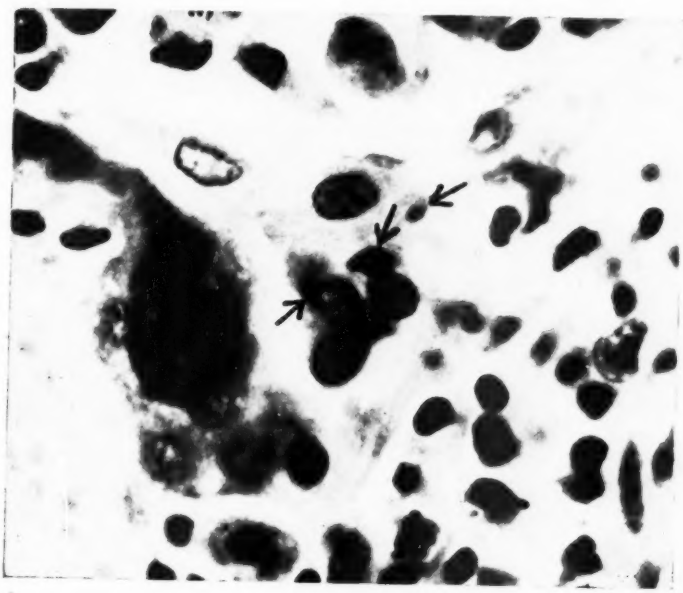

Pinkerton, Smiley and Anderson Giant Cells in Pneumonitis

PATHOLOGY OF SCLERODERMA, WITH SPECIAL REFERENCE TO THE CHANGES IN THE GASTROINTESTINAL TRACT*

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Numerous case reports and a few reviews on scleroderma have appeared in the literature and it does not seem justifiable to add other cases unless they present features which have not been previously emphasized. The following 2 cases are believed to be of interest because of lesions in the gastrointestinal tract that do not appear to have been described heretofore.

Scleroderma occurs in females twice as often as in males and most commonly in the fourth and fifth decades. Generalized and localized forms are recognized, the latter commonly known as morphea. The course of the disease may be rapidly or slowly progressive. Spontaneous recovery has been recorded, but is rare. The skin changes begin with edema and progress to induration and atrophy. In the latter stage the integument is of satiny smoothness and is tightly stretched over the bony prominences. Increased pigmentation of both exposed and unexposed parts of the body is often present. Pigmentation of the mucous membrane is practically never seen. Raynaud's syndrome may precede the sclerodermal lesions. Pain and a sensation of stiffness in the joints and muscles are common complaints and may be followed by joint and tendon contractures which are apt to incapacitate the patient. Sclerodactylia, ulceration of the skin, and osteoporosis of the bones of the extremities are common. Clubbing of the extremities has likewise been noted.

That scleroderma is not a disease of the skin alone but a generalized process has been realized for some time. Hektoen,[1] in 1897, described atrophy of the thyroid gland with endarteritis and hyperchromatophilia of the pituitary body, myocardial hypertrophy, and interstitial myocarditis. He attributed only the changes in thyroid and pituitary glands to scleroderma. Later, Matsui [2] reviewed the clinical and pathologic findings in 6 cases and emphasized the vascular lesions that occur in various localities.

The following case reports describe the clinical findings in our 2 patients:

Case 1

H. B., a housewife, 36 years old, of Polish extraction, was admitted to Goldwater Memorial Hospital on December 18, 1941, complaining of thickening of the

* Received for publication, February 4, 1944.

skin, pain on walking and poor appetite of about 15 months' duration. She stated that her mother had had similar skin lesions at approximately the same age, but had recovered completely. The patient had had the usual childhood illnesses without sequelae and had married at 26 years. In the next 5 years she had borne 3 children. In 1939, 2 years after the birth of her last child, when she was 33 years of age, she noted the presence of abdominal striae for the first time. These became more pronounced in the following year, when she experienced mild pains in the joints of the hands and feet, extending eventually to the knees and shoulders. During this period the patient felt cold, her appetite was poor and she lost 26 lbs. The skin over the extremities became swollen and movement was difficult.

On September 25, 1941, she had been admitted to the Presbyterian Hospital. At that time she was well developed and well nourished, the skin was deeply tanned, cool and dry, and smoothness and thickness of the skin were noticeable over the face, the anterior part of the chest and over the hands and feet. All the joints of the fingers were contracted and clubbing was present. She was unable to lift the right arm above the head. There was slight pitting edema of the legs and thighs. The abdominal striae were now prominent. The blood pressure was 110/70 mm. Hg. The patient was placed on a salt-free diet for 1 week, during which time the serum carbon dioxide, chlorides, calcium, sodium and nonprotein nitrogen values were within normal limits. Except for this interim, she remained on a high caloric, high vitamin diet. Medication included brewers' yeast, padutin,* crude liver extract, nicotinic acid, depropanex,† vitamin E and pancreatin. Physiotherapy was also employed. During her stay of 11 weeks she was seen by several ophthalmologists because of lateral nystagmus. This was attributed to congenital optic atrophy of unknown cause.

She was transferred to Goldwater Memorial Hospital in an unimproved condition on December 18, 1941. During the following year there was little change except for an additional loss of 15 lbs. in weight. She received 0.1 gm. of dry thyroid gland every day for several weeks. The skin lesions were slowly progressive. In November, 1942, she was forced to remain in bed because of weakness and stiffness of her extremities. In December, 1942, the patient complained of abdominal cramps for the first time. By April, 1943, this had become her predominant complaint and was associated with periods of nausea, vomiting and constipation. The patient was transferred to the surgical service on July 10, 1943, because of signs of intestinal obstruction. Many attempts to pass a Miller-Abbott tube were unsuccessful. Wangensteen drainage with a Levine tube was continued for 2 weeks but the patient became dehydrated. As soon as oral feeding was resumed, vomiting ensued. Occasionally this was induced by the patient herself for the relief of symptoms. Temperature ranged between 97° and 100.2° F. The blood pressure never rose above 112/80. She became gradually weaker and died on September 21, 1943. Necropsy was performed 26 hours post-mortem.

Gross Examination

The body was that of an emaciated white female, 36 years old. The scalp was freely movable, its hair dry, thin and covered by fine bran-like deposits. The skin of the face was smooth, shiny and tightly stretched across the underlying skeletal framework. The neck was long, thin and deeply tanned, the integument immobile. The abdomi-

* Padutin is a pancreatic tissue extract marketed by Winthrop Chemical Co., Inc., New York, N. Y.

† Depropanex is a pancreatic tissue extract marketed by Sharpe & Dohme, Philadelphia, Pa.

nal striae were white and contrasted strongly with the surrounding dark brown skin. The skin over the surface of the abdomen was desquamated in scales. Both the ventral and dorsal aspects of the trunk were light brownish or brownish yellow, the ventral surface being more deeply and extensively pigmented than the dorsal. The most intensely pigmented areas commenced at the lower third of the forearms and extended to the fingertips. Similar pigmentary altera-

	BLOOD	URINE	BLOOD CHEMISTRY VALUES	X-RAY	MISC.
Presbyterian Hospital 9/25/41 to 12/18/41	RBC 3,700,000 Hgb. 60% WBC 6,900 P. 80% L. 14% M. 5% E. 1%	Record not available	Phosphatase 5.1 B. U. Phos. 3.5mgm.% Ca. 9.7 " " NPN 22 " " Total cholest. 155 " " Free " 49 " " Esters " 106 " "	Trophic changes typical of scleroderma hands and feet. Normal sella turcica. Flat plate of abdomen normal.	B.M.R.+ 0 Stool normal. E.K.G. normal.
Coldwater Memorial Hospital Admission 12/19/41		s.g. 1.022 alb. 1+ occ. WBC	Urea N 9.1mgm.%		
7/12/43			Urea N. 32mgm.% Chlorides (as NaCl) 528 " " Total prot. 7.38 " " Alb. 4.8 " " Glob. 2.5 " "	G. I. Series: Periduodenal adhesion. Indirect evidence of obst.lesion at duodenal jejunal flexure. Barium enema: Generalized dilatation of entire colon without evid. of obst. lesion. Chest: Heart not enl.	B.M.R.46 E.K.G.1° ht. block PR .24sec Right bundle branch block. V.P C., L.A.D.
9/20/43	RBC 3,200,000 Hgb. 77% WBC 10,100 P. 88% L. 8% M. 4% E.S.R. 51 mm/hr.	s.g. 1.013 alb. 4+ WBC 8/HPF RBC 3/HPF No casts	Urea N. 35 mgm.%	Heart enlarged to left. No pleural effusion. No infiltration or consolidation. Moderate congestion.	E.K.G. same as 7/12/43

Text-Fig. 1. Table I presenting laboratory data for case 1.

tions were present in the lower extremities, and the tissue covering the dorsal aspects of the feet was edematous, pitting on pressure. No pigmentary changes were present in the visible mucous membranes. The upper and lower extremities were in a position of semiflexion because of contraction of the biceps and hamstring tendons. The muscle tissues of all extremities were extremely atrophied and the skin covering them was tense. The nail beds were broadened to almost twice their normal width, and the nails were convex. There were many decubiti over the dorsal surface of the trunk, one of which had penetrated the sacrum and was filled with blood. Small encrusted areas of ulceration lay over the interphalangeal joints, which were flexed. Free joint motion was secured when linear incisions were made into the skin covering

the dorsum of the toes. The joint capsules appeared to be normal. Section of the skin covering the palms and soles revealed almost complete absence of fat pads.

The breasts and intercostal muscles were markedly atrophied. On opening the chest each pleural cavity contained 300 cc. of clear serous fluid. The lungs together weighed 655 gm., and were feathery and crepitant throughout except at the extreme bases where they were deeply congested.

On opening the pericardium 15 cc. of cloudy, straw-colored fluid escaped. The pericardial sac was obliterated by adhesions over an area corresponding to about two-thirds of the cardiac surface. On stripping these adhesions the surface of the heart presented a granular appearance (Fig. 1). The heart weighed 240 gm. All valves were thin and delicate. The endocardium of the left ventricle, especially near the apex, was opaque and thickened. The myocardium was firm, brownish, and presented a wax-like appearance. The iodine test for amyloid was negative. On section the myocardium was found to be streaked by fine grayish bands of tissue which seemed to enter both from the epicardial and endocardial surfaces. These streaks were present with noticeable frequency in the interventricular septum in an area corresponding to the position of the conduction system.

The muscle tissues of the anterior abdominal wall were thin, and the overlying skin was thickened but freely movable. The peritoneum enclosed 700 cc. of straw-colored fluid. The visceral layer was thin, gray, smooth and glistening. The parietal layer was thickened. The gastrointestinal tract was of normal caliber throughout. No mucosal lesions were noted but the mucosa of the jejunum and ileum was deep brown.

The kidneys together weighed 225 gm. The surfaces were smooth. The cortices measured 0.8 cm. The cortical striations were distinct. A few glomeruli could be distinguished as pinpoint-sized gray dots. The medullae were congested.

The thyroid was small and on section presented a light brown surface streaked with whitish lines.

The remaining organs, including the parathyroids, pituitary body, adrenals, brain and cord, liver, spleen, pancreas, the bones of the skull, the ribs and vertebrae, showed nothing of note in the present connection.

Histologic Examination

Skin. The surface of the skin was covered by deposits of keratinized material. The epidermis was atrophied, the rete pegs slender and short. In the cells of the basal layer, pigment was present in greatly increased

quantities. The derma was thickened and edematous (Fig. 2). The subcutaneous fat was divided into lobules of irregular size by wide bands of connective tissue. The remaining fat showed the changes incident to serous atrophy and was diffusely infiltrated by lymphocytes and plasma cells. Occasionally small deposits of calcium were apparent in the collagenous fibers. The various appendages of the skin were surrounded by bands of coarse connective tissue. Similar bands surrounded many of the nerve fibers and blood vessels as well as the corpuscles of Vater and Meissner. The sweat glands, although atrophic, showed no constriction by collagenous tissue. The arrectores pilorum were hypertrophied and only occasionally encroached on by fibrous tissue. The lumina of the medium-sized arteries were narrowed by concentric layers of fibrous tissue in the intima. The internal elastica was often fragmented. Less conspicuous alterations were present in the form of fibrous replacement and hyalinization of the media. The smaller arteries and the arterioles, mainly in the areas of serous atrophy of fat, were thickened and presented a smudged appearance due to fibrinoid necrosis. Occasionally the lumen was obstructed by swollen endothelial cells. No thrombi were observed. In general, where the connective tissue fibers of the skin were coarsest, the elastic fibers were scarce. In the subcutaneous fat there was a fringe of fibrils along the borders of the collagenous bands.

The diaphragm, the intercostal muscles and those of the abdominal wall were atrophic. The striations were well preserved.

Thyroid. The thyroid was richly penetrated by fibrous bands which appeared to originate in the sclerotic capsule. At the periphery the organ was diffusely infiltrated by lymphocytes. The acini were small, uniform in size and filled with colloid. The cuboidal epithelial lining was well preserved. The blood vessels were embedded in thick connective tissue bands and the lumina of many of them were narrowed.

Heart. In the epicardium were bands of fibrous tissue together with fresh fibrinous deposits, polynuclear leukocytes, lymphocytes and plasma cells (Fig. 3). The parietal pericardium was similarly involved. Bacteriologic culture of the pericardium was sterile. The myocardium was traversed by connective tissue bands, many of which were perivascular. Almost all of the medium-sized and smaller arteries showed eccentrically thickened walls and narrowed lumina due to intimal fibrous tissue proliferation. There were ill-defined focal areas of fibrosis, in the midst of which were a few fairly well preserved muscle fibers. These areas were well vascularized and cellular (Fig. 4). The endocardium was tremendously thickened by overgrowth of fibrous tissue which practically replaced all of the trabeculae carneae, only a

few degenerate muscle fibers remaining. This tissue was richly infiltrated by polymorphonuclear leukocytes, lymphocytes, and plasma cells. Clumps of light brown, iron-free pigment were scattered through the affected areas (Fig. 5).

Lungs. The walls of the alveolar septa were thin and the alveoli contained serous fluid and desquamated cells. The periphery of the lower lobes was extensively fibrosed. The fibrous tissue was richly vascularized and was especially abundant around the blood vessels and smaller bronchi. In these areas many of the alveoli were lined with tall columnar, mucus-containing cells which were continuous with those of the terminal bronchioles.

Gastrointestinal Tract. Throughout its entire extent the mucosal layer of the esophagus was replaced by fibrillar, acellular tissue to which a few red blood cells were adherent. Beneath, and sometimes mingled with it, were bands of muscle tissue representing the remains of the inner longitudinal layer. Many of these fibers showed fibrinoid degeneration but no cellular infiltration between them. The submucosa was composed of dense collagenous tissue. The circular muscle was almost completely replaced by fibrous tissue, isolated fibers persisting as islands lying in edematous fibrosed and vascularized areas. The longitudinal fibers were few in number, thin and atrophic. The myenteric plexuses of Auerbach were carefully studied but no deviation from the normal was found. The serosal layer was edematous and fibrotic (Figs. 6 and 7). Except for some edema and atrophy of the muscularis, the stomach appeared to be well preserved. The mucosa of the jejunum showed diffuse lymphocytic infiltration. The villi enclosed masses of hemosiderin. The submucosa contained many dense collagen fibrils but was not thickened. Both muscle layers were atrophied. In many places the muscle layer was so extensively replaced by bands of fibrous tissue that the mucosal surface was brought into close approximation with the serosa. The mucosa and submucosa of the appendix were hyalinized and the lumen reduced to a slit-like aperture. The vessels were greatly thickened and hyalinized. The muscularis was atrophic. The changes in the colon were similar to those in the small intestine. The lesions described were patchy in character. The vascular changes in the gastrointestinal tract were slight but the serosa was fibrotic and thickened throughout (Figs. 8 and 9).

Mesentery. A thick layer of connective tissue covered the peritoneal surface. The nerves and vessels were encased in fibrous tissue and the fat was reduced. One medium-sized artery showed a narrowed lumen due to intimal proliferation and edema, and infiltration by lymphocytes (Fig. 10).

Kidneys. The majority of the glomeruli were damaged. A few were hyalinized, others necrotic, while still others showed the so-called "wire-loop" appearance. Often the glomeruli and Bowman's space contained polymorphonuclear leukocytes and red cells which extended into the proximal convoluted tubules. The predominating vascular lesions were in the arteries of small caliber and consisted of: (1) intimal edema and proliferation; (2) widespread necrosis of the muscularis or of the entire wall; and (3) hyalinization with narrowing of the lumen. Combinations of these lesions might be seen in the same vessel. The walls of the arteries and the edematous interstitial tissues were infiltrated by polymorphonuclear leukocytes, lymphocytes and plasma cells. The tubules contained many casts of different types and the tubular epithelium was crowded with hyaline droplets. The walls of the pelves were markedly fibrotic and the vessels showed much the same lesions as those in the parenchyma although there were, in addition, perivascular connective tissue bands.

Cervix. The uterine cervix showed an area of erosion. The lamina propria was diffusely thickened at the mucocutaneous junction by coarse and heavily vascularized connective tissue. The thin-walled vascular channels were surrounded by bands of fibrous tissue. Deep in the cervical wall the medium-sized arteries showed the proliferative endarterial changes described elsewhere. Bands of perivascular connective tissue also outlined the thick-walled vessels.

Histologic examination of the remaining organs, including the parathyroids, adrenals and pituitary body, liver, spleen, pancreas, fundus uteri and ovaries, showed nothing of note in the present connection.

Anatomic diagnoses included: generalized scleroderma; acute fibrinous and chronic pericarditis; fibrosis of endocardium and myocardium; pleural effusion, bilateral; ascites; edema of feet; diffuse glomerular and arterial lesions of the kidneys; muscular atrophy of the gastrointestinal tract; degeneration of esophageal mucosa; minimal pulmonary fibrosis; multiple decubiti; muscular atrophy; atrophy of thyroid; partial degeneration of optic nerve, chiasm and tracts.

Case 2

W. K., a car draftsman, 56 years old, presented himself at the Vascular Clinic of the New York Post-Graduate Hospital on May 12, 1942. He said that he had been in excellent health until August 21, 1941, when, following the ingestion of frankfurters, he experienced an episode of diarrhea, puffiness of the face and ankles, and muscle pains. The white blood count at the time was said to be elevated and to contain 8 per cent eosinophils. No muscle tissue was removed for biopsy. Skin tests for trichinosis were negative. In December, 1941, the patient noticed that his hands and feet were often stiff and cold. This condition became progressively worse so that in January, 1942, he was forced to give up work. Two months later

the stiffness had progressed to involve the skin of the entire body. At this time a piece of skin was removed for biopsy and was reported as showing "some predominance of fibrous tissue." At the Vascular Clinic it was noted that the skin over the entire body was taut, dry and deeply pigmented. Joint motion was limited because of contractures of the skin. The blood pressure was 110/70 mm. Hg, the peripheral pulses were of good quality, and oscillometric readings were normal.

Treatment included mecholyl * iontophoresis, depropanex and dihydrotachysterol.

The patient attended the clinic until June 16, 1942, when he was admitted to the Post-Graduate Hospital and remained until July 10, 1942. During this period he complained for the first time of difficulty of swallowing and of a dull, midepigastric pain which had no relation to meals. He also developed a cough productive of white mucoid sputum.

	BLOOD	URINE	BLOOD CHEMISTRY VALUES	X-RAY	MISC.
August, 1941 to May, 1941	RBC 4,490,000 Hgb. 86% WBC 15,450 P. 82% L. 14% M. 2% E. 2%	Routine — normal. No arsenic in 24 hr. spec.	NPN 28.5 mgm.% Creat. 1.16 " "		
Post Graduate Hospital 5/12/42 to 7/12/42	Wassermann — negative.	Several — normal.	Phos. 6.2 mgm.% Ca. 10.2 " " Urea N. 10.5 " " NPN 29.5 " " Chlorides (as NaCl) 485 " " Glucose 80 " " Cholest. 195 " " " esters 115 " "	Chest: Moderate ht. enlargement—mainly left vent. Mod. hilar root branch thickening mainly toward bases. Sl. pleuritic thickening left costo-phrenic sinus.	Vit. C. saturation normal. B.M.R.+6
	RBC 4,780,000 Hgb. 72% WBC 17,000 P. 68% L. 21% M. 8% E. 12% B. 1%	Addis count: Vol. 190 c. c. Ph. 5.3 Casts 74,100 RBC 47,550 WBC 110,200			
7/9/42		Urinary steroids 277 mgm./24 hr. 17 ketosteroids 4.8 mgms. Routine — faint tract alb., 1-2 hyalin/HPF 1-3 gran./HPF			
Goldwater Memorial Hospital 7/10/42 to 7/17/42		Normal	Urea N. 43 mgm.%	Bilateral pleural effusion ext. into fissures and a sl. generalized enlargement of heart.	E.K.G.—L.A.D. Low voltage in lead II P. R. interval .16 sec.

Text-Fig. 2. Table II presenting laboratory data for case 2.

The physical findings were unchanged. He was comfortable when lying in bed, and fairly well nourished despite the loss of an unknown amount of weight. The heart was not enlarged to percussion. There was a soft apical systolic murmur and the sounds were of good quality. The lungs were clear; the abdomen was difficult to palpate because of the density and inflexibility of the skin. The left epididymis was slightly thickened. There was no edema. The skin and joints were as previously described. The blood pressure varied between 120/80 and 90/70 mm. Hg. The temperature ranged from 99.2° to 100.8° F.

When the patient entered Goldwater Memorial Hospital on July 10, 1942, his blood pressure had risen to 158/100, and he died suddenly 1 week after admission.

* A proprietary name for acetyl-β-methylcholine chloride.

Gross Examination

The body was that of a fairly well developed and nourished white male, 56 years of age. The skin over the shoulders, forearms, hands, abdomen and feet was deeply pigmented and inelastic. Almost the entire body covering was affected. The fingers and toes were held in semiflexion by the stretched, unyielding integument. On section the skin was thickened and the subcutaneous fat traversed by bands of white fibrous tissue. The intercostal muscles in the second left space were extremely thin and the pleura could be seen beneath the fascia.

The right pleura enclosed 250 cc. of amber fluid; the left, 150 cc. The left lung weighed 470 gm. The pleural surface was opaque. The lung felt airless. On section it cut with great resistance. The substance of the lung was increased by fibrous tissue. The right lung weighed 640 gm. and presented essentially the same naked-eye appearances as the left. The increased density of the lungs was more striking in the lower two-thirds than in the upper one-third, which was moderately congested and edematous.

The pericardium contained 50 cc. of amber colored fluid. The heart weighed 350 gm. The epicardium was thick and opaque. The parietal pericardium was similarly thickened. The endocardium of the right side of the heart was thin and glistening. The endocardium of the left ventricle was opaque and thickened, particularly on the posterior and septal walls. The myocardium was brown, flabby and showed ill-defined grayish areas. About 2 cm. from its origin the caliber of the anterior descending branch of the left coronary artery was slightly reduced because of subintimal plaques.

No lesions were noted in the esophagus.

On opening the abdomen about 100 cc. of amber fluid was found. The musculature was thin and flabby. Both layers of the peritoneum were thick and white, and numerous adhesions bound the viscera together.

The intestine was of normal caliber. The stomach was dilated.

The right kidney weighed 170 gm.; the left, 180 gm. The capsules stripped with difficulty leaving irregular granular surfaces in which yellowish nodules projected against a dark purple-red background. The cortices were narrowed, the striations indistinct.

The thyroid was small, light brown and showed almost no colloid on section.

The rest of the organs revealed nothing worthy of note in the present connection.

Histologic Examination

Skin. The epithelium was atrophic. Small amounts of pigment were present in the basal layer. The derma showed clumps of extracellular melanin and was edematous and thickened. The subcutaneous connective tissue was coarse, avascular and contained only a few fat deposits. The walls of the smaller arteries and of the arterioles were edematous and surrounded by bands of fibrous tissue. A few areas of necrotizing arteritis were present in them. The hair follicles, the arrectores pilorum and the sebaceous glands were buried in dense constricting bands of connective tissue. The sweat glands were atrophic, but otherwise unchanged. In the scalp the arrectores pilorum were hypertrophic. Many of the medium-sized arteries and the arterioles in the deeper layer of the derma were occluded by fibrotic proliferation and edema of the walls. In some arteries all vascular coats had been penetrated by red blood cells from the lumen.

Striated Muscle. Sections from muscles in various parts of the body showed atrophy of the individual fibers with retention of the striations and some proliferation of sarcolemmic nuclei. Occasionally the fibers were swollen and fragmented and the nuclei were pyknotic. No Trichinella were seen (Fig. 11).

Heart. The epicardium was fibrous throughout and, over the surface of the right ventricle, hyalinized. Cellular infiltration of the epicardium varied in degree, and was predominantly lymphocytic in character. In the myocardium were ill-defined areas of fibrosis, many of which were continuous with the endocardium while others occurred in the midst of relatively well preserved muscle tissue. The centers of the latter lesions were well vascularized by minute blood channels surrounded by lymphocytes. The endocardium of the left ventricle showed a few patchy areas of thickening. The smaller arteries were encircled by fibrous bands, but only a few of them were edematous with their lumina narrowed.

Lungs. Sections of all lobes revealed very marked increase in fibrous tissue. The alveoli were widely replaced by richly vascularized and hemorrhagic fibrous tissue. The pleural surfaces were extensively fibrotic. The larger arteries of the parenchyma showed only a small amount of subendothelial fibrosis. Almost without exception the walls of the smaller arteries and of the arterioles were greatly thickened by edematous fibrous tissue and swollen endothelial cells. In many instances the lumina of the arterioles were almost completely obliterated (Fig. 12). Section of the right lower lobe showed an acute pneumonic process.

Thyroid. Except for a solitary, circumscribed, adenomatous nodule

the thyroid was poor in colloid and was diffusely infiltrated by lymphocytes which, in places, were so dense as to obscure the parenchyma. There were several small nodules composed of Hürthle cells. Surrounding these areas the parenchyma was largely replaced by tall proliferating epithelial cells and lymphocytes. Intravesicular papillary projections were rare. The greater part of the parenchyma was fibrosed.

Gastrointestinal Tract. The entire stomach wall was less than half the normal thickness. The mucosa was intact, the muscularis mucosae thin and in many places replaced by fibrous tissue, and the submucosa was composed largely of coarse connective tissue fibers. The muscle layers were atrophic. The serosa was slightly thickened.

The submucosa of the intestines contained numerous coarse connective tissue fibers. The muscularis mucosae was occasionally thinned. Marked edema separated the muscle layers. In many places the muscle layer was replaced by fibrous bands in both the circular and longitudinal layers. The plexuses of Auerbach appeared to be large in contrast to the atrophic muscle.

The peritoneum was thickened, its blood vessels dilated and congested. An infiltration of lymphocytes extended from the peritoneum into the surrounding fat tissues. The intima of some of the larger arteries was thickened. The arterioles shared the edema of the surrounding tissues.

Kidneys. The glomeruli were small. Many were congested, others bloodless. Some showed areas of fibrinoid necrosis, others had thickened capillary walls; a few were hyalinized. In some of the loops the limiting membrane was hyalinized; in others the capillaries were dilated and contained large numbers of polynuclear leukocytes. In some instances the glomerular spaces enclosed red blood cells extending into the proximal convoluted tubules. The interstitial tissue was increased, especially in the region of the glomerular capsule where it was infiltrated with polynuclear leukocytes, lymphocytes and eosinophilic myelocytes. The tubular epithelium was poorly preserved, most of the cytoplasm being granular. In the tubules were many casts of various types. In practically every medium-sized and small artery advanced fibrinoid necrosis involved the entire wall. A few polynuclear leukocytes and lymphocytes were present in such areas. In some vessels the lumina were obliterated by the necrotizing process, while in others edema and separation of the collagenous fibers produced narrowing of the lumen. In some, necrosis was confined to the muscular coat (Figs. 13 and 14). The renal pelves were thickened by coarse connective tissue fibers beneath intact epithelium.

Prostate. Sections showed adenomatoid hyperplasia. In addition, the walls of the vessels at the periphery were fibrotic. In several areas the smooth muscle fibers were atrophic.

Anatomic diagnoses included: generalized scleroderma; necrotizing and proliferative arteritis; pulmonary fibrosis; hydrothorax, bilateral; dilatation of heart; coronary sclerosis, mild; myocardial fibrosis; chronic passive congestion of liver; diffuse glomerular and arterial lesions of kidney; atrophy of thyroid; atrophy of intercostal muscles, and muscular atrophy of gastrointestinal tract.

Discussion

The cause of scleroderma has been variously ascribed to infectious and toxic, neurogenic, endocrine and vascular disturbances. The interrelationship of scleroderma with dermatomyositis, disseminated lupus erythematosis, the Libman-Sacks syndrome and polyarteritis nodosa is adequately discussed by Banks.[3] MacCallum[4] and Klemperer, Pollack and Baehr[5] have suggested an alteration in the colloidal system of the connective tissue as the factor which offers the most promising field of investigation.

In case 1 of this report the predominant complaints for the last 5 months of the patient's life were referred to the gastrointestinal tract. Clinical and roentgenologic evidence seemed to point to obstruction of, and disturbance in, the pattern of the mucosa of the small intestine. Barium enemas indicated irregular muscular contractions and diffuse dilatation of the colon. In case 2, late in the course of the disease, the patient developed dysphagia and complained of midepigastric pain.

The histologic changes were impressive in the gastrointestinal tract and appeared to explain the clinical findings in this report. The mucosa of the esophagus in case 1 was completely replaced by fibrinoid material, the submucosa was sclerotic, the muscle layers atrophic and extremely fibrosed. Rake[6] also has called attention to loss of the esophageal mucosa in scleroderma. In his case the submucosa was infiltrated by lymphocytes and polynuclear leukocytes so that the inflammatory nature of the lesion could not be denied. Recently, Lindsay, Templeton and Rothman[7] have recorded 3 cases of stricture of the esophagus in scleroderma in which tissue removed for biopsy revealed ulceration of the superficial epithelium and dense infiltration of the immediately surrounding tissues by neutrophils, eosinophils and plasma cells. In one of the cases here recorded there was no cellular infiltration in spite of the fact that the patient had a Levine tube in position for long periods; therefore it seems that the lesion of the esophagus should be attributed to scleroderma and not to trauma produced by the tube.

Thickening of the submucosa, and fibrosis and atrophy of the muscularis have been noted by many observers.[7-10] Cases have been recorded with esophagoscopic and roentgenologic evidence of obstruction at the lower end of the esophagus, but none of these has been confirmed by necropsy. It would appear that such lesions are due to spasm and that, as the muscle atrophies, spasm ceases. This may account for the improvement which has been noted after dilatation and sympathectomy. The remainder of the gastrointestinal tract in both cases here recorded showed extensive, although patchy, changes. Thickening of the submucosa was not a particularly prominent feature in either case. Diffuse dilatation of the colon demonstrated by barium enema in case 1 may be explained by deficiency of smooth muscle. Matsui [2] mentioned hypertrophy of the muscularis mucosae but atrophy of the muscularis propria. In my cases either no change in the muscularis mucosae or atrophy was observed. Edema was present in the muscularis adjacent to areas of muscle atrophy. This latter change is in accord with the general pattern of the disease as it is seen in the skin in the form of edema, induration and atrophy. Vascular alterations in the gastrointestinal tract were not conspicuous.

Lesions of the gastrointestinal tract in scleroderma, with the exception of those described in the esophagus, have received little attention. A third patient with diffuse scleroderma, who was under observation for 3 years in the Goldwater Memorial Hospital, developed signs of intestinal obstruction. Adhesions between intestinal loops were found at operation. No point of obstruction was determined but the small intestine was diffusely dilated. Death followed 12 hours later. Permission for necropsy was not obtained.

In case 1 of this report pericarditis was present and appeared to be both recent and old. According to Lewin and Heller,[11] pericarditis was present in 8 of 29 cases observed at necropsy. In view of the fact that some of these cases were associated with other conditions, notably tuberculosis and rheumatism, it is difficult to say whether the accompanying pericarditis can be attributed to scleroderma. In the cases here described the lesion in the pericardium presented hyalinization of collagenous tissue which was reconcilable with the lesions of scleroderma in other parts of the body. In case 1 the acute lesion overlying the chronic fibrous pericarditis was diffuse and too advanced to be included among those related changes which sometimes occur in uremia. In view of the fact that there were similar thickening and hyalinization of other serous membranes, particularly the peritoneum, it seems justifiable to include those in the pericardium as part of the disease, scleroderma, and not as manifestations of the uremic state.

The endocardial and vascular changes were more severe in case 1. The myocardial lesions were of like intensity. In both cases electrocardiograms showed left axis deviation and, in case 1, right bundle branch block. Clinically, neither patient showed any signs of cardiac insufficiency. Because most of the changes in the heart in scleroderma have been described in detail by Weiss, Stead, Warren and Bailey,[12] there is nothing to be added except to record the widespread vascular lesions observed in the medium-sized and small-sized arteries of the myocardium.

Although extensive pulmonary fibrosis was present in case 2, clinical signs were negligible, the patient having complained only of mild dyspnea on exertion. The anatomic lesions were out of all proportion to the clinical and roentgenologic findings. The vascular alterations in the lungs were more extensive than those found elsewhere. However, in case 1 the changes were confined to the periphery of the lungs at the bases, and were of slight degree. Even here the perivascular and peribronchial fibrosis seemed to represent sclerodermatous change. Linenthal and Talkov [13] have reported 3 cases with extensive changes in the lung, as revealed by roentgenologic examination together with clinical signs of pulmonary insufficiency and Raynaud's syndrome. Although fibrosis of the lung is frequently described in generalized scleroderma, practically no mention is ever made of pulmonary insufficiency.[2, 12, 14]

The thyroid was one of the first glands to be implicated in considering the pathogenesis of scleroderma. In case 1 the changes in the thyroid consisted of moderately increased fibrous tissue and proliferative lesions in the arteries. In case 2 the changes were more extensive and involved the architecture of the entire gland. Clinically, the patients showed no signs of disturbed thyroid function.

Parathyroids were available for examination only in case 1. They appeared to be normal, but it was noted that one of the branches of an artery supplying the gland showed proliferation in the intima. No changes were seen in the bones with the exception of osteoporosis of the fingers in case 1. In both cases the serum calcium and phosphorus were normal.

The pituitary body has been thought by some to be the seat of dysfunction in scleroderma, hyperchromatophilia and areas of necrosis having been described in the anterior lobe. In neither of our cases were changes observed other than those of post-mortem autolysis.

The adrenals have been incriminated in scleroderma largely because of bronzing of the skin. Unlike Addison's disease, pigmentation of the mucous membranes has not been mentioned. In the majority of cases

observed at necropsy the adrenals appeared to be normal. In the 2 cases reported here no structural alterations were noted in the adrenals although both patients exhibited rather intense pigment deposits in the skin. Neither patient had received x-ray therapy.

In both of the cases here recorded extensive renal lesions were found, especially in the medium-sized and smaller arteries. The glomerular lesions were similar to those observed in lupus erythematosis. Tubular alterations were severe. The renal pelves in both cases were thickened. The larger vessels in the peripelvic fat showed the same sort of perivascular fibrosis as that observed in other parts of the body. Compared with the histologic alterations, clinical signs and laboratory data indicating renal disease were slight.

Uterine atrophy has been noted by several observers. In case 1 no such change was found. On the other hand, the lamina propria of the vagina and the external cervical os shared in the generalized connective tissue thickening that occurred in the skin and elsewhere. The ovaries appeared to be normal.

Although it is difficult to estimate the amount of smooth muscle in the prostate, in case 2 it appeared to be atrophic. This may represent a sclerodermal lesion rather than an involutional change. Except for proliferative changes in the intima of the arteries the testes were normal.

Many studies have been made of scleroderma and its possible relationship to dermatomyositis.[3, 12] However, the borderline is not clear. In case 1 the changes in the skeletal muscles were slight and were attributable to atrophy from disuse. In the other case the muscle changes were somewhat more severe, but in neither case were infiltrations of lymphocytes present as in dermatomyositis, nor was there extensive muscle damage characteristic of that disease.

The changes in the skin were the same as those customarily encountered in scleroderma; namely, increase of connective tissue, atrophy of fat, edema, vascular lesions, calcinosis, atrophy of epithelium and increased pigmentation.

Changes in the central nervous system were studied extensively by Dr. Abner Wolf and were not considered noteworthy in the present connection.

Unfortunately, the sympathetic ganglia were not studied. The sympathetic plexuses in the gastrointestinal tract showed no structural alteration.

Whether lesions of the sympathetic system are responsible for the spasm exhibited roentgenologically in the gastrointestinal tract awaits

investigation. To date, the results of sympathectomy for Raynaud's syndrome in patients who develop scleroderma have been variable and not encouraging.

Conclusions

In two cases of generalized scleroderma endocardial and myocardial fibrosis, widespread vascular alterations, pulmonary fibrosis and severe kidney lesions were found, in addition to the usual dermal alterations. These changes were more severe than the clinical course of the disease and the laboratory data indicated.

Evidence is presented to include pericarditis as a manifestation of scleroderma.

Scleroderma is not a disease marked by connective tissue overgrowth alone, but also includes muscle degeneration and atrophy with or without connective tissue replacement. The severity of the muscle changes bears no direct relationship to the lesions of the vascular system.

The muscle atrophy throughout the gastrointestinal tract and replacement of the mucosa of the esophagus by fibrillar material are integral parts of the disease, scleroderma, and are related to some of the symptoms and signs observed during life.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 5

FIG. 1. Case 1. Heart with extensive pericarditis.

FIG. 2. Case 1. Skin of chest wall showing atrophic, deeply pigmented epidermis, and thickened derma and subcutaneous tissue. There is a connective tissue band about the atrophic hair follicles. × 160.

FIG. 3. Case 1. Epicardium with fibrinous exudate on surface, and fibrosis and cellular infiltration of the deeper layers. × 30.

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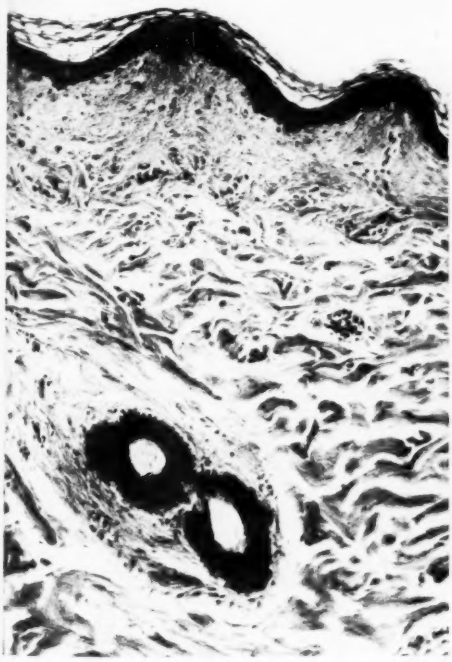

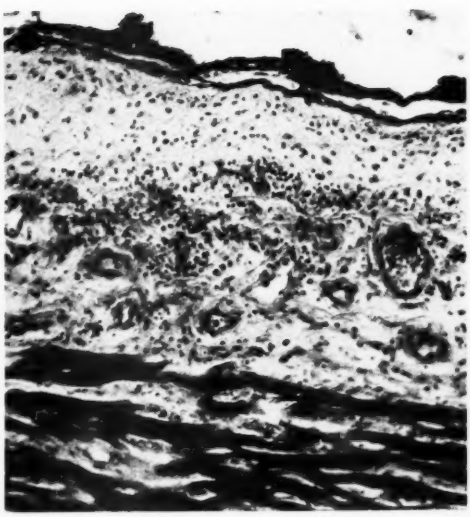

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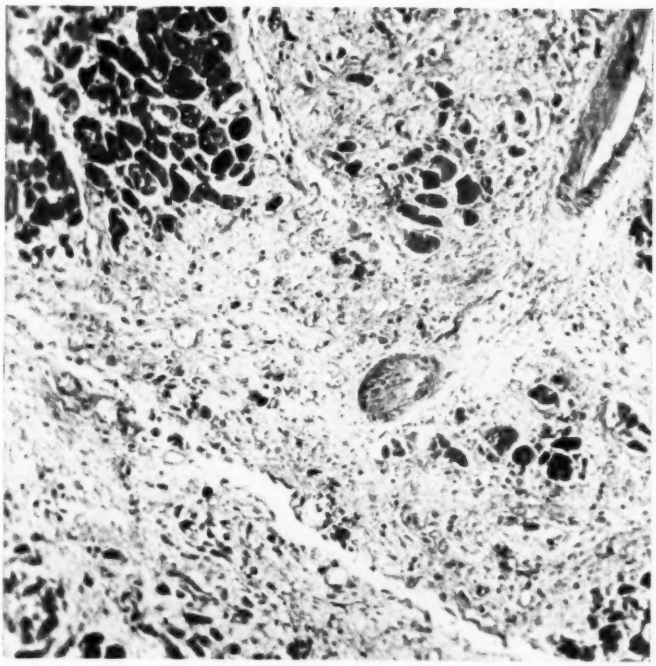
Scleroderma

PLATE 6

FIG. 4. Case 1. An area of myocardial fibrosis in which a vessel with thick, partially necrotic walls can be seen. × 172.

FIG. 5. Case 1. Endocardium with areas of thickening by fibrous tissue, which also extends into and partially replaces the muscle. Trichrome stain. × 31.

FIG. 6. Case 1. Esophagus with fibrillar material on mucosal surface, a thick fibrotic submucosa and extensive fibrous replacement of the muscle layers. Trichrome stain. × 31.



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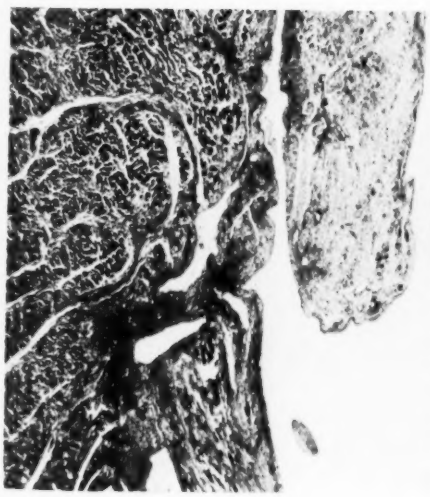

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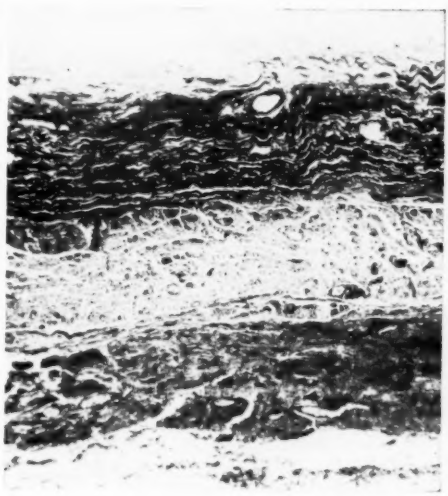

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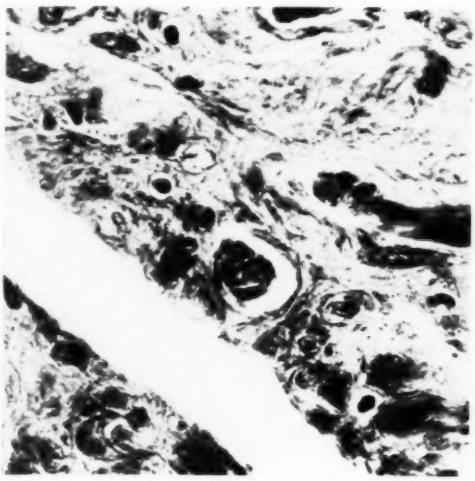
PLATE 7

FIG. 7. Case 1. Higher magnification of muscularis of esophagus showing atrophic muscle fibers. Trichrome stain. × 972.

FIG. 8. Case 1. Section of the intestine showing loss of the longitudinal muscle at the left, and edema and atrophy of circular muscle. Trichrome stain. × 38.

FIG. 9. Case 1. Another section of the intestine with only a narrow band of fibrous tissue joining mucosa and fibrotic, thickened serosa. Trichrome stain. × 30.



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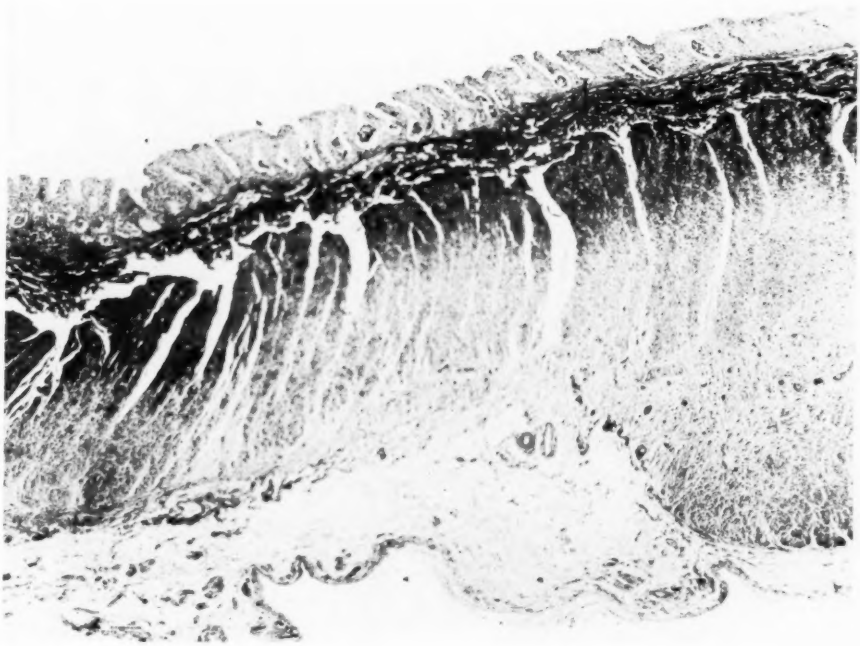

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PLATE 8

FIG. 10. Case 1. Mesenteric artery illustrating fibrous tissue proliferation, lymphocytic infiltration and edema of intima, and reduplicated internal elastica. Elastic tissue stain. × 1075.

FIG. 11. Case 2. Striated muscle showing disintegration of fibers. Hematoxylin and eosin stain. × 450.

11

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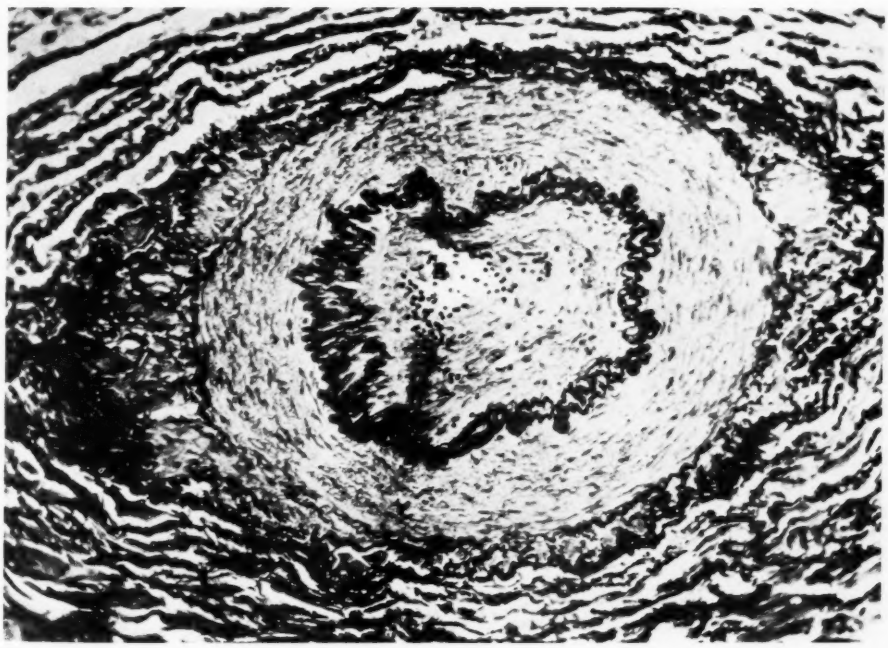

Bevans Scleroderma

PLATE 9

FIG. 12. Case 2. Small, thick-walled arteries and extensive replacement of alveoli of lung by fibrous tissue. In the few alveolar spaces which remain are desquamated cells. Hematoxylin and eosin stain. × 172.

FIG. 13. Case 2. Kidney showing partially necrotic glomerulus, pronounced arterial lesions, and a few casts. Hematoxylin and eosin stain. × 120.

FIG. 14. Case 2. Renal artery with necrosis of the muscularis, proliferation of the intima and penetration of the wall of the vessel by red blood cells. Hematoxylin and eosin stain. × 290.

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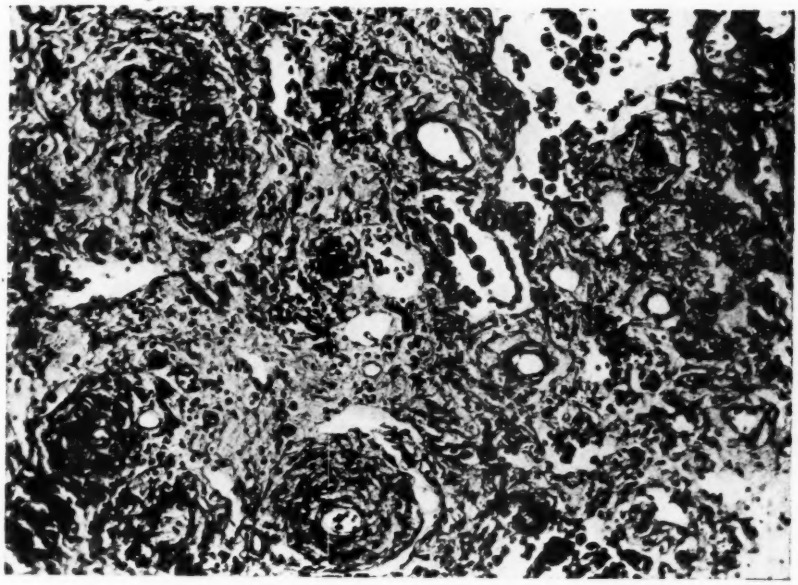

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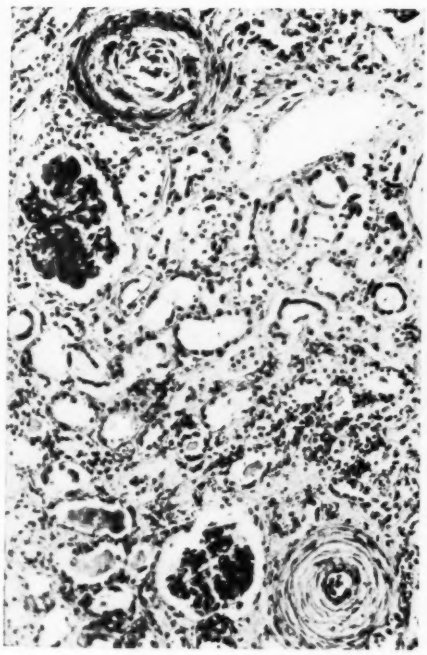

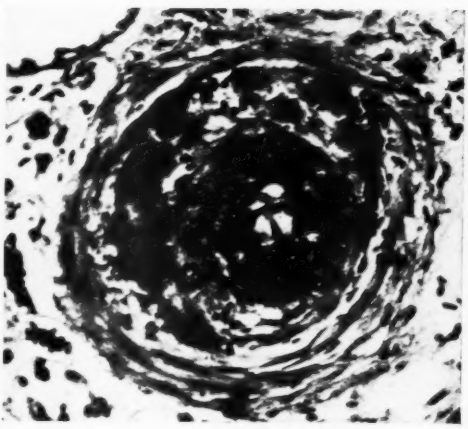

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Scleroderma

HETEROLOGOUS MESODERMAL TUMORS OF THE UTERUS
REPORT OF A NEOPLASM RESEMBLING A GRANULOSA CELL TUMOR *

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Heterologous tumors of the uterus are not extremely rare. By far the most common neoplasms in this group are the mixed mesodermal tumors which occur in both the body and cervix of the organ.[1] At present, it is impossible to say with certainty whether the tumors occurring in the cervix differ fundamentally from those confined to the fundus. Pathologically, they are very similar.

Mixed mesodermal tumors are monodermal in origin and should be distinguished from the trigerminal teratomas, which are extremely rare. Morphologically, the former are sharply demarcated polypoid growths which occupy a submucosal position in the uterus and are composed of heterotopic malignant cells of various types. Embryonic myxomatous tissue is present in all of these tumors, and in many of them hyaline cartilage, striated muscle, bone and fat are to be seen. Many of the cells are well differentiated and the degree of malignancy is out of all proportion to the histological appearance. The prognosis is uniformly grave, most of the patients succumbing during the first year.

Many theories regarding the origin of these neoplasms have been proposed. The simplest explanation is that of neoplastic metaplasia.[2] However, it is extremely unlikely that adult tissues normally present in the uterus can be dedifferentiated into mesodermal derivatives which are normally not seen in that organ. Wilms [3] is of the opinion that these tumors arise from undifferentiated mesodermal cells which are displaced from the lumbar region during the descent of the Wolffian body. Lebowich and Ehrlich [4] have objected to this theory on the basis that no proved cases of this type of tumor have been reported as having developed along the course of the Wolffian ducts. In the light of our present knowledge, it appears most likely that these tumors originate from indifferent mesodermal cells which have retained their capacity for differentiation into mesodermal tissues of various types.[5]

Several case reports of tumors of this type are to be found in the recent literature, and excellent reviews of the subject have been given by Lebowich and Ehrlich,[4] Glass and Goldsmith [6] and Liebow and Tennant.[7] The purpose of this paper is to report the unusual case of a heterotopic mesodermal uterine neoplasm which possessed all of the morphological characteristics of a granulosa cell tumor. The case is of

* Received for publication, February 14, 1944.

interest further in that it affords additional support for the contention of Fischel,[5] and others, that the granulosa cells are derived from the mesenchyme and not from the celomic epithelium as is ordinarily taught.

Report of Case

A white female, 44 years old, was admitted to the North Carolina Baptist Hospital on January 25, 1943, complaining of menorrhagia, a sense of pressure in the lower abdomen, and leukorrhea which was exaggerated immediately following menstruation.

She began menstruating at the age of 16 years and her periods occurred every 28 days with a duration of from 4 to 6 days. About 3 years before, she began to menstruate more frequently than formerly, and the interval between periods was reduced to 24 days. Concurrently, an increase in the duration and amount of flow was noted, menstruation now lasting from 6 to 8 days. She had been pregnant seven times and had had two miscarriages and five normal deliveries.

The physical examination revealed a fairly thin woman in no apparent distress. Her temperature was 37° C.; pulse, 87 per minute; respirations, 22 per minute; and blood pressure, 180 mm. of Hg systolic, 78 diastolic. The thyroid gland was normal in size and position. The breasts were atrophic and no masses were felt. On auscultation a soft apical systolic murmur was heard. Positive physical signs were not elicited from the lungs. The abdomen was soft and there were no masses or tenderness.

Pelvic examination revealed normal external genitalia and a parous outlet. A cystocele and rectocele were present. The uterus was normal in size and was freely movable; a third degree retroflexion was present. No masses were palpable in the adnexa. The cervix showed slight erosion around the external os but was otherwise not remarkable.

The hemoglobin was 76 per cent (Sahli) and the leukocyte count showed 5,200 cells per cmm. The studies on the urine were not revealing.

A vaginal hysterectomy and posterior repair were done under spinal anesthesia by Dr. G. C. Cook on January 27, 1943. The ovaries were normal in size and the left one contained a thin-walled cyst, 1 cm. in diameter, which was ruptured at the time of operation and was found to possess a smooth lining and to be filled with a clear fluid. The adnexa were otherwise normal.

The patient had an uneventful postoperative course and was discharged on the 17th hospital day. A follow-up examination 11 months after operation showed her to be free from her previous symptoms. No palpable masses were present in the pelvis at this time.

Pathological Examination

The specimen consisted of the entire uterus, which measured 11 by 6 by 5 cm. in its greatest dimensions. The cervix was large and boggy and the vaginal surface was smooth, except for an area immediately adjacent to the external os where irregular areas of reddish brown discoloration were seen. The external surface of the body and fundus was smooth and glistening. The endometrial cavity was found to be filled with blood. Attached to the fundus on its posterior surface was an oval-shaped, firm nodule which was covered by endometrium and measured 2 cm. in diameter. It was well encapsulated and occupied a submucosal position. The endometrium covering the tumor and im-

mediately adjacent to it measured 1 mm. in thickness, while elsewhere it varied from 2 to 3 mm. The myometrium averaged 2 cm. in thickness and was without evident gross lesions. On sectioning, the tumor was found to be yellow and moderately firm; heavy, grayish white bands radiated throughout its substance.

Serial sections of the entire neoplasm revealed in every instance a well circumscribed and encapsulated tumor which occupied the submucosal position (Fig. 1). The myometrium immediately adjacent to the tumor was atrophic but otherwise presented no abnormalities (A in Fig. 1). A careful search was made for extracapsular tumor cells but none could be found.

The endometrium which covered the tumor, and that immediately adjacent to it, was thin and atrophic, and the longitudinal axes of the glands were parallel to the surface (B in Fig. 1). Elsewhere, the endometrium was hyperplastic and composed of numerous irregular glands which were situated in active interstitial tissue. The glands were thickened and were frequently composed of several layers of cells. In most instances the tumor was sharply demarcated from the remaining endometrium, although at several points considerable intermingling of tumor cells and endometrial stroma was noted.

The tumor was composed of groups of epithelial cells which were separated from each other by irregular bands of connective tissue. These bands radiated throughout its substance and frequently showed hyalinization. In many instances the parenchyma and stroma were so arranged as to form diffuse sheets of epithelial cells and not infrequently they presented a cylindromatous pattern (Figs. 2 and 3). A definite tendency toward rosette formation was clearly demonstrated in many areas (Fig. 4). The epithelial cells possessed large, darkly staining nuclei with scant cytoplasm. These cells were morphologically identical with granulosa cells and were more or less uniform in appearance. An occasional mitotic figure was seen. Varying degrees of luteinization were present in different areas, and clusters of cells showing extensive vacuolization were scattered throughout the neoplasm (Fig. 5).

At several points a sharp line of demarcation could not be drawn between the tumor proper and the endometrium. At these points the tumor cells were intimately associated with the mesodermal cells making up the endometrial stroma. These mesodermal cells appeared to possess embryonic properties, and differentiation into both epithelial and spindle cells could be seen. In many instances within the endometrium proper there were formed clusters of rosettes which were com-

posed of lutein-like cells, some of which displayed vacuolization (Fig. 6).

Laidlaw's method for the demonstration of reticulum was employed. The epithelial cells were found to be devoid of fibrils, and the cylindromatous pattern previously noted was now even more pronounced (Fig. 7). Spindle-shaped cells could be seen among the argyrophilic fibers, which communicated freely with one another.

Frozen sections stained with scharlach R revealed large quantities of sudanophilic fat, which occupied an intracellular position. Additional material examined with the polariscope was not doubly refractive and was probably neutral fat.

Discussion

The most frequent heterologous tumor occurring in the uterus is the so-called mixed mesodermal tumor. It is probable that these tumors originate from pluripotential mesodermal cells which differentiate into one or more structures ordinarily originating from the mesoderm. There exists at present considerable confusion regarding the exact criteria to be satisfied before a tumor can be placed in this group. This is evidenced by the fact that, in independent reviews appearing in 1941, Glass and Goldsmith [6] accepted from the literature 94 tumors as mixed mesodermal neoplasms of the uterus, while Lebowich and Ehrlich [4] would admit only 12. The latter authors, following the example of Läwen,[8] insisted on the presence of striated muscle in the tumor for it to be acceptable. Since these tumors represent a distinct pathological entity and follow a rather typical course clinically, it would appear unwise to exclude the majority of them on rather arbitrary histological criteria.

In rare instances, heterotopic tumors appear in the uterus which are identical morphologically with neoplasms occurring characteristically in organs quite remote from that structure. Schiller [9] described a tumor occurring in the uterus of a woman, 47 years old, which was morphologically identical with the ordinary ovarian dysgerminoma.

The case we have reported represents the first recorded instance of a neoplasm originating within the uterus which was morphologically identical with a granulosa cell tumor. The possibility of such an occurrence has, however, been suggested by Schiller, and others. Extraovarian granulosa cell tumors are extremely rare. Ragins and Frankel [10] have described a large intraligamentous granulosa cell tumor which was removed from a Negress, 37 years old, who presented no evidence of tumor in her ovaries. Voigt [11] has reported a retroperitoneal granulosa cell tumor which occurred in the absence of neoplastic disease in

the ovaries. Walthard and v. Werdt,[12] Klaften[13] and Fauvet[14] have each described retroperitoneal recurrences following the removal of granulosa cell tumors from the ovary. Schiller[15] is of the opinion that these tumors arose independently of the ovarian neoplasms and had their origin in mesodermal rests which had remained retroperitoneal and had not come in contact with the ovary. Clinical evidence in favor of this concept is found in the complete cures which have followed the removal of recurrent neoplastic tissue. Such cures are not obtained in other recurrent ovarian carcinomata.

Most investigators are now of the opinion that the granulosa cells are derived from the mesenchyme and not from the germinal epithelium, as has been the orthodox teaching for many years. Histogenetically, our tumor is best explained by assuming an origin from mesodermal cells that had retained their potentiality for producing granulosa cells in adult life. In this case, as in others, the stimulus for tumor formation remains unknown.

Summary

Heterologous mesodermal tumors occurring in the uterus are not extremely rare. They are usually of the mixed variety and are best explained histogenetically by assuming an origin from pluripotential mesodermal cells which have remained dormant and for some unknown reason assume neoplastic properties.

Occasionally, mesodermal tumors are found in the uterus which are identical with neoplasms originating characteristically in other situations. Such a tumor is the dysgerminoma of the uterus reported by Schiller.[19]

In this paper the first case of a neoplasm originating in the uterus, which was morphologically identical with a granulosa cell tumor of the ovary, has been reported. It is presented as evidence against the view which is prevalent among many morphologists that the granulosa cells arise from the celomic epithelium.

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DESCRIPTION OF PLATES

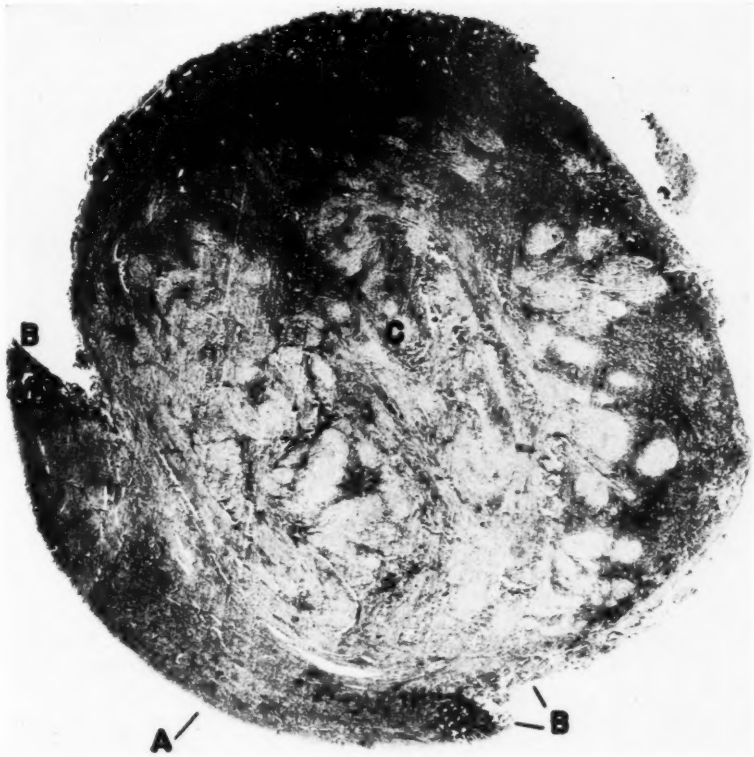
PLATE 10

FIG. 1. A section through the entire tumor, which includes the adjacent myometrium. (A) Myometrium. (B) Endometrium. That portion which covers the tumor is thin and atrophic. (C) Tumor. × 7.

FIG. 2. Large groups of epithelial cells are seen and in certain areas there is a tendency towards a cylindromatous arrangement. × 90.

FIG. 3. A higher magnification of an area seen in Figure 2. × 320.

1



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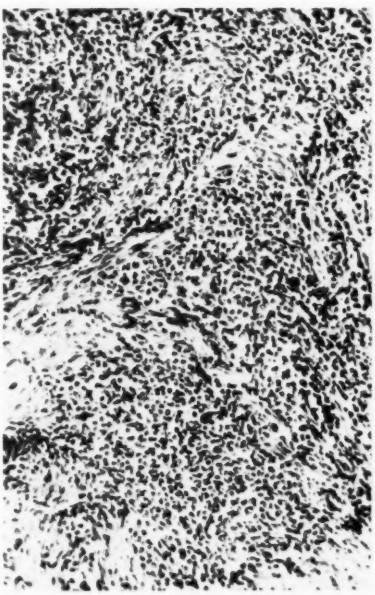

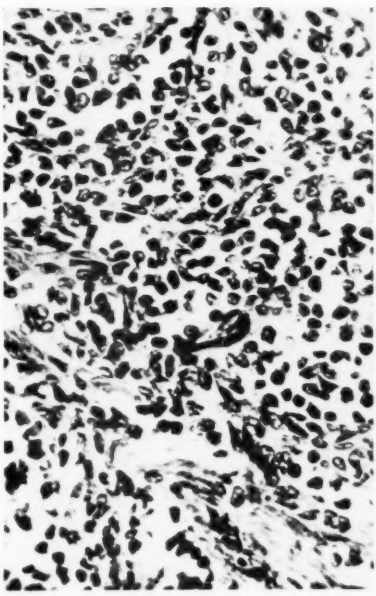

3

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PLATE 11

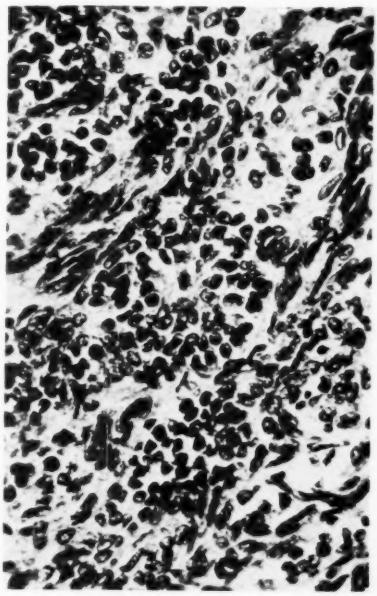
FIG. 4. A well formed rosette is seen in the center of the photograph. × 320.

FIG. 5. A group of epithelial cells, many of which contain neutral fat, are incompletely limited by dense fibrous tissue. Certain of the vacuolated cells show an alveolar grouping while others are scattered diffusely throughout the tumor. × 100.

FIG. 6. An area intimately associated with the endometrium. Mesenchymal cells here appear to be differentiating into both epithelial and spindle-shaped cells. The lutein-like cells are arranged in a characteristic grouping. × 90.

FIG. 7. Section stained for reticulum, showing the characteristic cylindromatous pattern and the absence of fibrils in the parenchyma. × 100.

4



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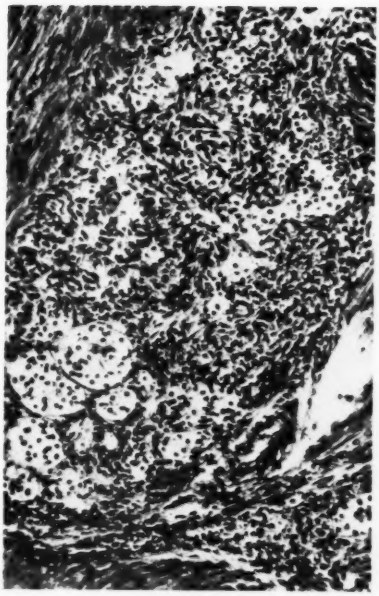

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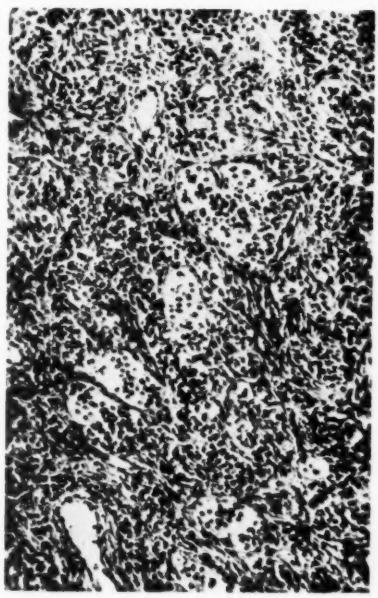

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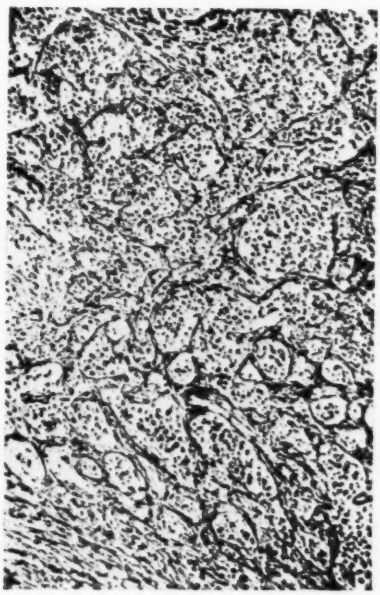

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Heterologous Tumors of the Uterus

ADENOMATOID TUMORS OF THE GENITAL TRACT*

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Fifteen cases of a tumor with definite anatomic features, limited to the epididymis, testicular tunics and the serosal surface of the uterine tube, have come to our attention in the past 2 years. A survey of the literature makes it probable that the same tumor has been seen and described by others under a variety of names (see "Discussion" below). Hinman and Gibson [1] (1924), Thompson [2] (1936) and Scalfi [3] (1936), in their reviews of the literature on tumors of the epididymis, spermatic cord and testicular tunics, agree that reported tumors of these sites are uncommon, and that those of the epididymis are exceedingly rare. However, in the past several years isolated case reports and reports of small series of cases have appeared in which the clinical and gross findings, the microscopic reports, and photomicrographs appear to be identical to those of the tumors to be described. Inasmuch as the reported series is still small, even in the aggregate, we believe it important to report our findings in this group of 15 cases, the largest series studied to date.

CLINICAL AND PATHOLOGIC ASPECTS

In Table I there are summarized the salient features of the reported clinical findings and the topographic anatomy, and in Table II, the notable pathologic features of this tumor group.

From a consideration of the data contained in the tables the following condensation of the clinical details is possible: All but 2 of the tumors were present in males ranging from 20 to 68 years of age. Most patients were in the third and fourth decades of life. In only 1 of the 2 cases in females could the age be ascertained and in that instance it was 67 years. The tumor was discovered on routine physical examination, or as an incidental post-mortem finding or surgical finding, presumably without previous symptoms in 6 cases; and was associated with pain or tenderness, either with or without exertion, at the local site in 8 instances. Progressive increase in size was noted in 5 cases, usually on the basis of the patient's own testimony. A history of trauma was part of the clinical record in only 2 cases. In those instances where the tumor was discovered only incidentally, on either recorded physical examination or at operation for some other complaint, or at the autopsy table, there was, of course, no way of knowing how long it had been present; but when the patient did know of the tumor's presence, the shortest reported period prior to operation

* Received for publication, February 21, 1944.

TABLE I

Clinical Data on 15 Cases of Adenomatoid Tumors of the Genital Tract

A.M.M. Accession*	Sex	Age	Race	History, symptoms and signs	Location, topographic anatomy and source
97945	M	29	W	Discovered on routine physical examination. No symptoms noted.	Lower pole of the epididymis. Sharply demarcated nodule 1.5 cm. in diameter.
94094	M	23	W	Patient discovered a pea-sized, freely movable nodule in the region of the rt. testicle. There was pain locally on exertion. In 6 mos. there was a progressive increase in size up to 2 cm. in diameter.	Adherent to the tunica vaginalis, exact site not specified.
84615	M	28	W	History of blow to rt. testicle 10 yrs. before operation. Five yrs. later a small pea-sized swelling was noted which grew slowly in the last 1½ yrs. Another injury caused increase of mass to goose-egg-size with subsidence in 3 wks. Recent rapid growth to 2.5 cm.	In the "epididymis, independent of the testicle."
81346	M	32	W	Incidental finding in varicocele operation.	"Supernumerary body on the left testicle."
84648	M	26	W	Small growth in upper pole of left testicle with pain, of 3 yrs.' duration, with no increase in size. Onset attributed to blow to region.	Upper pole of testicle.
76268	M	44	W	Patient noted swelling, 10 yrs. prior to operation, in region of lt. testicle, with subsequent slight, gradual increase in size. Complaints of regional tenderness after long standing or walking. A pea-sized nodule present for 5 yrs. prior to operation.	Lower pole of epididymis.

TABLE I (Continued)

Clinical Data on 15 Cases of Adenomatoid Tumors of the Genital Tract

A.M.M. Accession*	Sex	Age	Race	History, symptoms and signs	Location, topographic anatomy and source
97904	M	21	W	Tumor of rt. testicle present for "some time." Tender to pressure and painful on sudden movement.	Lower pole of epididymis.
94348	M	26	W	Painful tumor in left side of scrotum of 8 mos.' duration, with threefold increase of size during that time.	Lower pole of epididymis. Shelled out easily at operation.
91983 A–36–1427†	F	67	W	Incidental autopsy finding.	Uterine tube.
S–13031‡	F	?	C	Incidental finding at operation.	"Encapsulated tumor on fallopian tube."
S–692‡	M	33	W	Duration and symptoms unknown.	Mass about the size of a bean was dissected away from the region of the rt. testicle.
S–15463‡	M	34	W?	Mass in region of testicle, known to be present for 3 yrs. prior to operation.	Tumor on the surface of the tunica vaginalis over the lower pole of the testis.
A–2633‡	M	68	C	Incidental autopsy finding.	Lower pole, lt. epididymis.
100648	M	22	C	Patient noted a small, tender nodule at the upper pole, lt. testicle, 2 wks. prior to operative removal. No history of trauma or infection.	Tumor nodule involving only the "capsule" of the upper pole of the lt. testicle.
101680	M	38	W	Nodule present in scrotum for 5 yrs., with very gradual increase in size during that time. Painful "at times."	Nodule in the globus minor of the epididymis.

* All cases except those noted below are from the Army Institute of Pathology, Army Medical Museum, and represent cases submitted through U. S. Army Medical Department sources. All cases have been incorporated in The General Tumor Registry, a subdivision of The American Registry of Pathology, The National Research Council, housed at the Army Medical Museum.

† Contributed by Dr. A. A. Nelson, Washington, D.C., from the Autopsy Series, University of Minnesota, School of Medicine, Department of Pathology.

‡ Contributed by The Division of Pathology, The National Institute of Health, Bethesda, Md.

TABLE II

Gross and Microscopical Observations on 15 Adenomatoid Tumors of the Genital Tract

A.M.M. Accession	Gross morphology	Microscopic morphology	Special stains	Notes
97945	Circumscribed, white firm tumor mass 1.5 cm. in diameter.	Mixed gland types. Mainly microfollicular, partly macrofollicular, and scanty, solid, cord-like formations. Fibrous stroma.	Fat stains (sudan IV in isopropyl alcohol) and mucicarmine stains negative in all cases for stainable material in the vacuoles or gland lumina. Best's carmine method for glycogen stained negatively in all cases, using formaldehyde-fixed tissue, or the paraffin blocks prepared from formaldehyde-fixed tissue as the *only* source material. Reticulum stains showed a well defined perifollicular meshwork in all cases. Phosphotungstic acid hematoxylin stains showed well defined cell borders without processes in the lining cells of the gland-like groups. The presence of smooth muscle bundles in some of the sections was confirmed by Masson's trichrome stain.	Serologic tests for syphilis, and routine blood counts were not contributory in any case.
94094	Dumbbell-shaped nodule 2.6 × 1.3 × 0.8 cm. in size. A thin capsule invested the whole. The cut surface was smooth, homogenous, translucent, and bulged slightly.	Mainly macrofollicular. Stromal background is dense, fibrous.		
84615	Encapsulated, globular, firm, elastic nodule, 2.5 cm. in diameter. The cut surface was grayish pink with irregular coarse areas of grayish white, and the whole had a whorled, fibrous appearance.	Mixed gland types: microfollicular, macrofollicular, and solid cord-like formations Small lymphocytic nodules present in the periphery. Fibrous stroma.		
81346	Portion of resected epididymis which overlay and partially enveloped a firm, gray, roughly spherical nodule within it, measuring 1.2 cm. in diameter. The mass appeared circumscribed and probably encapsulated.	Macrofollicular type predominantly. Diffuse, light, lymphocytic infiltration in a predominantly fibrous stroma.		
84648	Resected testicle, epididymis, and spermatic cord. An irregular, apparently circumscribed nodule was present, lying between the head of the epididymis and the base of the spermatic cord, without any evidence of invading regional tissues.	Mainly of the solid cord-like type, with occasional microfollicular formations. Stroma dense, fibrous.		
76268	The resected tail of the epididymis was found to be indurated. Cut section revealed a spherical, hard nodule 1.2×1.0 cm., which did not appear to be encapsulated. The cut surface was white and glassy, with faint yellow flecking.	Macrofollicular type predominantly. Stroma loose and fibrous.		No recurrence or metastasis 4½ yrs. after operation. Aschheim-Zondek test negative prior to operative removal.

				moval.

TABLE II (Continued)

Gross and Microscopical Observations on 15 Adenomatoid Tumors of the Genital Tract

A.M.M. Accession	Gross morphology	Microscopic morphology	Special stains	Notes
97904	Poorly circumscribed nodule of firm, white, neoplastic tissue, measuring 1.0 cm. in greatest diameter, which encroached on regional testicular tissue without evidence of invasion.	Mainly microfollicular. Slight diffuse lymphocytic infiltration in the fibrous stroma, and an occasional small lymphocytic interstitial nodule.		
94348	Encapsulated, smooth gray-white nodule measuring 1.5 × 1.2 cm. Cut surface white, firm, tough.	Mainly microfollicular. Dense collagenous stroma. Large bundles of smooth muscle present in the periphery. Occasional interstitial lymphocytic nodule present.		
91983, A–36–1427	None available. Reconstruction from microscopic picture is that of a nodule extending from the serosa through the thickness of the tubal wall.	Mainly macrofollicular. Fibrous stroma.		
S–13031	"Encapsulated tumor in fallopian tube."	Mainly macrofollicular. Fibrous stroma.		
S–692	Mass about size of a bean dissected from region of "rt. testicle." (Microscopic section shows it to be epididymal.)	Microfollicular and solid cord-like types. Fibrous stroma.		
S–15463	Tumor nodule appearing as a part of the tunica vaginalis. The cut surface was "fibroid in character."	Mainly macrofollicular. Stroma partially fibrous with bundles of smooth muscle chiefly in the periphery. A few small clusters of lymphocytes and a slight diffuse spread of them are present interstitially.		
A–2633	Circumscribed, dense yellowish mass in the inferior pole of the epididymis, which is "walled off."	Mainly macrofollicular, and to a lesser degree microfollicular. Mainly fibrous background. Small number of smooth muscle bundles in the periphery.		
100648	Oval mass of pinkish gray tissue 0.5 cm. in diameter in "capsule" of testicle. Cut surface shows gray, faintly nodular, glistening, resilient tissue.	Mainly solid cord type. Partially encapsulated. Diffuse, slight, round-cell infiltration interstitially.		
101680	Globus minor of the epididymis received in which there was a firm, hard nodule, 1.0 cm. in diameter, which was partially encapsulated.	Mainly macrofollicular. Number of smooth muscle bundles chiefly in the periphery of the tumor. Numerous interstitial lymphocytic nodules. Moderate diffuse lymphocytic interstitial infiltrate.		

was 2 weeks and the longest 10 years. The size estimated by the surgeon or medical examiner was usually larger than the recorded gross dimensions as determined by the pathologist. The clinical appreciation of size probably took into consideration more than the tumor proper, possibly enlargement of the regional tissues consequent to blood and lymph stasis.

The following appears to be a reasonable composite gross description of this tumor group: The growths tend to be small, the largest in this series measuring 3 by 2 by 1 cm., the smallest, 0.5 cm. As a rule the tumor is globular, circumscribed and firm even to the point of induration. On section the cut surface varies from white to yellowish or pink and is glistening and may show either a smooth or finely fibrous stroma. (In one instance it was reported as being finely nodular.)

In our series the tumor was found either in the epididymis, the tunics of the testicle, or the serosal surface of the uterine tube. For tumors (2) from the last situation the gross descriptions are not available, but the microscopic sections show a neoplastic involvement, apparently growing into the underlying muscle coats from a superficial origin. In no instance was there any evidence, surgical or pathologic, of invasion of regional tissues or of metastases.

The microscopic anatomy of the tumors showed considerable variation. All of the tumors had a fibrous stroma varying from a loose collagenous meshwork to a dense, and in some instances, partially hyalinized fibrous stroma. Between the bundles of connective tissue, gland-like spaces were so distributed that fibrous stroma was present between all of them. Whatever the form of these glandular spaces their course lay in many directions, even in a single microscopic field. The glandular structures were of variable pattern, but the cell type was fairly characteristic. Some of the tumors tended to show a preponderance of one gland-like type over the other, but the rule was to find a variable picture, particularly in multiple sections. The variation in the gland-like structures was from almost solid cords (Fig. 2) of cuboidal and low-columnar cells to greatly dilated spaces lined by markedly flattened cells (Fig. 4). In Table II these are called "solid cord-like," "microfollicular" and "macrofollicular," respectively. In all of the tumors, examples of all types were seen. The majority of the cells contained vacuoles of variable size (Fig. 5), reaching exceedingly large proportions (Fig. 8), and producing a signet-ring appearance (Fig. 6). The vacuoles were always sharply demarcated. The nonvacuolated cells, best seen where the tumor formed cords, varied from cuboidal to low-columnar, had a finely granular, acidophilic cytoplasm, and a round or oval, centrally placed nucleus rich in chromatin. Cilia were

absent. No pigment was present in any of the cells. In many instances markedly vacuolated cells could be seen with only thin cytoplasmic strands connecting them (Fig. 6). In other places, gland-like spaces were lined by cells with shreds of cytoplasm still present along the free border (Fig. 7), suggesting gland formation by fusion of vacuoles. The gland lumina contained no material staining with hematoxylin and eosin, such as is seen in lymphangiomas. No blood cells of any kind were found within the lumina. This cell type is common to all of these tumors, as is also the pattern produced by these cells. This pattern is consequently considered the primary unit of structure for this tumor.

It was previously noted that the composition of the stroma was variable. Occasionally, bundles of smooth muscle were present in considerable quantity (Fig. 11). In none of these instances was the microscopic evidence convincing that the muscle was an integral part of the tumor. It appeared more reasonable to assume that the smooth muscle represented inclusion of pre-existing muscle in an expansile tumor growth.

An attempt was made to determine the nature of the vacuoles. Special stains for lipids were negative in all instances. The mucicarmine stain revealed neither mucinous granules nor mucin vacuoles in any of the sections. None of the material available for study had been preserved in ethyl alcohol. Therefore our attempts at staining these vacuoles with Best's carmine method for glycogen made use of formaldehyde-fixed wet tissue and/or the paraffin blocks prepared from formaldehyde-fixed tissue. The results were uniformly negative. The question, therefore, of the glycogen content of these vacuoles must remain open. The phosphotungstic acid hematoxylin stain revealed no fibrillar processes in any of the cells, even when they were present in solid cords, or when they lay in small clusters in the interstitial tissues. On the contrary, this stain revealed that the cell borders were well defined, smooth, and free of either brush borders or cilia. Reticulum stains showed a characteristic pattern of the reticulum meshwork (Fig. 10) rather intimately applied to the gland-like spaces in strands from one to three rows thick. There was no evidence of a basement membrane. The interstitial tissue contained a scattering of lymphocytes, with an occasionally admixed monocyte (Fig. 3). Plasma cells, eosinophils and neutrophils were absent. Occasionally, a cluster of lymphocytes produced a small nodule without a secondary center. Other portions of the same tumor, or other tumors, were without round cell infiltration. There was no evidence of the effects of chronic inflammation, such as scarring, adjacent to the lymphocytic foci. In none

of the sections studied was there any evidence of invasion of the regional tissues. Microscopically, the tumors could be shown to be either sharply circumscribed or encapsulated (Fig. 1). In most instances there was no marked compression of the regional tissues, suggesting that the rate of tumor growth was slow.

Discussion

Inasmuch as this tumor appears to be confined to the genital tract, origin from misplaced embryonic or fetal genital ridge is a tempting hypothesis. Accordingly, a number of testes and epididymides, with their adjacent tissues, from stillborn infants, and similar anatomic structures from fetuses, were subjected to frozen section study from slices made at close intervals. No structures resembling these tumors were encountered. There are no reports of cellular elements in the development of the embryonic genital ridge which resemble those of the tumor described above. It is conceivable that, since these tumors may arise from an abnormal group of genital ridge cells, the method of sampling employed is inadequate. One should examine a very large number of specimens before accepting or dropping such a postulate as to origin. The question of the tumor's genesis must remain open.

Differential Diagnosis

It is our impression that the tubular, acinar, follicular, or, at least, gland-like element of the tumor is composed of *epithelial* cells. The variation from low-columnar to flattened cuboidal cells growing with an epithelial cohesiveness is best illustrated in regions showing cord-like growth (Figs. 2 and 5). The tendency of these cells to develop vacuoles is another epithelial characteristic (Figs. 5 and 6).

Those authors who have considered the tumor endothelial in origin (Rigano-Irrera,[4] Charache,[5] Malisoff and Helpern,[6] Mercandier and Thomas[7]) appear to have accepted the flattened cuboidal appearance of the tumor where large spaces are formed as the cell type (Fig. 8). An examination of their photomicrographs and of our material shows an essential difference cytologically between these cells and endothelium elsewhere, even in angiomas. In the latter tumor group, lining endothelial cells preserve the typical endothelial, central nuclear bulge in a spindle-shaped cell which has sharply tapering ends. In our series of genital tract tumors the whole cell is flattened and never spindly.

Evans[8] proposed the reasonable hypothesis that these tumors are mesothelial in origin, because of their location on or near mesothelial surfaces either in the epididymis, tunics of the testicle or uterine serosa. Aside from the historic errors of oncologists in postulating mesothelial

origin to neoplasms of obscure origin, this hypothesis fails to explain the marked tendency towards vacuole formation and the gland-like special arrangement of cells. These properties are described neither for normal mesothelium nor for the more commonly accepted mesotheliomas, such as those of the pleura. Occasionally, one sees prominent mesothelium in various stages of inflammation, as in pleuritis, pericarditis and peritonitis. By using the comparison microscope it is clearly evident that the cells of this tumor are markedly different from even swollen mesothelial cells. In organizing or organized inflammations in such sites (pericardium, pleura or peritoneum) one may see pinched-off mesothelial cell clusters, still viable in a fibrous background. These, too, show marked cytologic differences when compared side by side with these tumor cells, and certainly show no tendency towards vacuolization. Finally, while it seemed obvious in Evans' series that there was an intimate serosal connection in his 4 cases,[8] no such clear-cut uniformity of continuity is present in our series of 15 cases.

The stromal background is variable, both in different areas of the same tumor and in different cases. The collagenous stroma may be of variable density. Smooth muscle may be present in isolated strands or in fairly heavy bundles. Our examinations convince us that both strands and bundles represent inclusions of neighboring muscular tissue. Therefore, a compound name such as mixed leiomyoma and lymphangioma (Malisoff and Helpern,[6] and Halpert [9]) does not appear justified. Similar objections may be raised against the designation "adenomyoma" (Sakaguchi [10] and Falconer [11]).

In a discussion of pseudo-tumors of the epididymis, Mark [12] described a similar tumor, judging by the text descriptions and the accompanying photomicrograph. He postulated a chronic inflammatory lesion as the basis for the histologic picture. While it is true that a diffuse lymphocytic infiltration and even nodular lymphocytic accumulations are present in these tumors, there is no other evidence of inflammation; nor do any of the known chronic inflammatory conditions of these genital structures result in such tissue alterations.

Thompson [2] and Hinman and Gibson [1] reported similar, if not identical, tumors and described them as adenocarcinomas of a low grade of malignancy. In our series there is no evidence of invasion of the regional tissue even in our cases of 10 years' duration. Follow-up information is available in only 1 of our cases (A.M.M. Accession 76268) where in 4½ years following removal there was no evidence of either recurrence or spread.

On the basis of our analysis it appears to us that the primary unit of the tumor is epithelial in nature and that it tends to form gland-like

spaces and, therefore, deserves the name adenoma, as is suggested by Gordon-Taylor and Ommaney-Davis,[13] and by Blumer and Edwards.[14] However, the genesis of the tumor is obscure. We cannot be certain that these elements arise from a pre-existing glandular structure. In the present state of our knowledge it is proposed that the designation *adenomatoid* be given to this tumor type. The proposed name has the advantage of being morphologically correct and genetically neutral.

Natural History of This Tumor Group

The first impression one receives in examining these tumors microscopically is frequently that of disorderly epithelial proliferation. In our series a diagnosis of malignancy was frequently made by the primary examiner. Clinically and pathologically the evidence favors benignancy. Where long periods intervened between discovery of the tumor and operation, there was no histologic difference in the tumor type as compared to those removed soon after discovery. One does not expect this sort of constancy in a malignant tumor. When first found at autopsy, or incidentally at operation, the tumors are fairly large without evidence of local invasion or distant metastases. Mitotic figures are very rare in all cases. The question as to whether these tumors can become invasive and metastasize in time cannot be answered from the data available. Most of the tumors grew slowly, according to the clinical data. The clinical description of a period of rapid growth immediately antecedent to surgical removal does not appear to be borne out by microscopic examination of the tissue. There is neither evidence of mitotic cellular proliferation nor of marked regional tissue compression such as would be the case in rapidly expanding tumors. As has been suggested, some of the clinical impressions of increased size may be due to partial compression or obstruction of venous or lymphatic return from the regional tissues, producing an increase of size in the area involved. A history of trauma and subsequent growth was present in 2 cases. The relationship to trauma is obscure and there is no evidence in regional tissues that trauma may have played a rôle. One does not find areas of fat necrosis or organized hemorrhage, for example. Furthermore, it should be noted that identical tumors were found in 2 instances in this series in the uterine tube, again without microscopic evidence of trauma.

Biologic Activity of the Tumor Group

In 1 of our cases the Aschheim-Zondek test was performed prior to surgical removal and was reported as negative. In the case reported by Malisoff and Helpern[6] a positive test was recorded, but in that case discussion brought out that it may have been a false positive test.

Summary

Fifteen cases of an apparently benign tumor of the genital tract in males and females are reported and the pertinent pathologic and clinical findings summarized. An argument has been presented for designating these neoplasms as *adenomatoid tumors. Adenomatoid tumors* of the genital tract have a well defined glandular pattern, as a rule, arranged spatially in many planes with considerable variation in size of lumina and cell structure. They may suggest malignant tumors on primary microscopic examination, particularly by the frozen section method. Both in our series and in reported cases there has been no evidence of malignancy if mitotic activity, local tissue invasion, and metastasis are considered. The clinical data also suggest the benign nature of the tumor group. The origin of this tumor is obscure.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

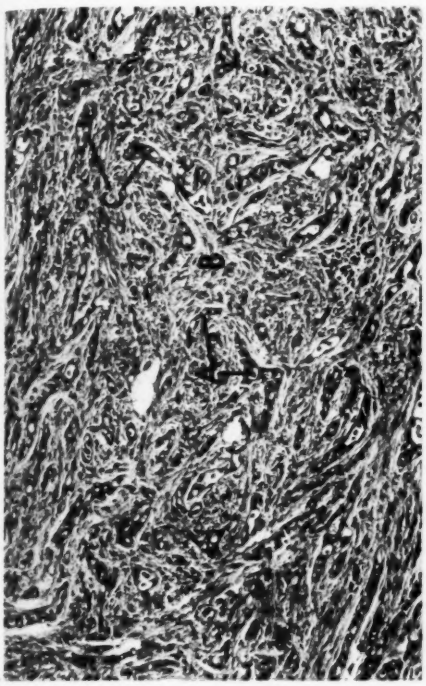
PLATE 12

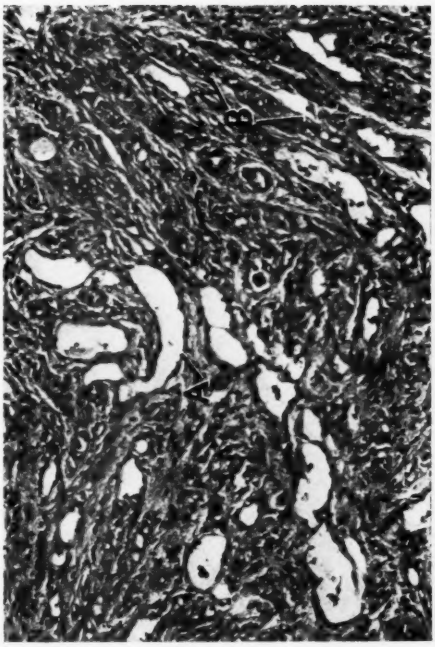
FIG. 1. Acc. 81346, Neg. no. 74712. Low-power view of the relationship of the tumor (A) to the epididymis (B). × 5.

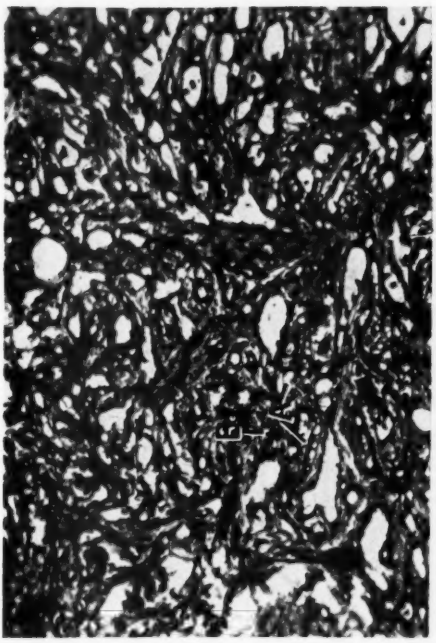
FIG. 2. Acc. 84648, Neg. no. 74708. There is a predominantly solid growth in cords (A) in a dense fibrous stroma (B). Vacuolated cells are seen at C. × 118.

FIG. 3. Acc. 84648, Neg. no. 74709. The tumor pattern is microfollicular. Vacuolated cells are seen at A; scattered lymphocytes at B. × 118.

FIG. 4. Acc. 84615, Neg. no. 74714. The pattern is chiefly macrofollicular (A). Solid cords of cells (B) are present also. × 118.







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Adenomatoid Tumors of the Genital Tract

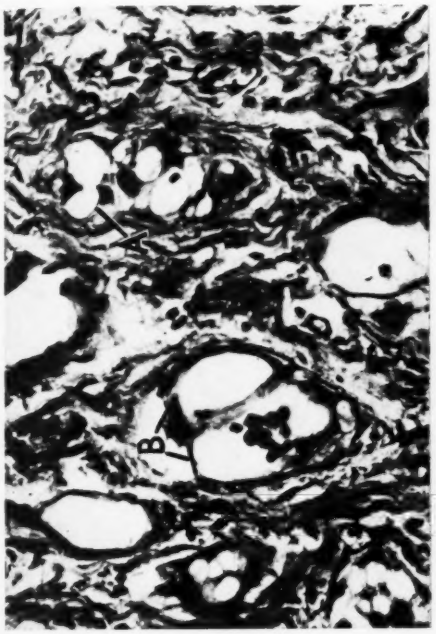
PLATE 13

FIG. 5. Acc. 84648, Neg. no. 74710. The vacuolated type of cell (A), of moderate size. × 395.

FIG. 6. Acc. 76268, Neg. no. 74705. Larger cell vacuoles producing signet rings (A), and very large, multinucleated vacuolated cells (B). × 395.

FIG. 7. Acc. 81346, Neg. no. 74711. A gland-like space (A) with cytoplasmic spurs along the free cell border. × 395.

FIG. 8. Acc. 84615, Neg. no. 74715. The cell type seen in the macrofollicular pattern. The whole cell is flattened, but is still cuboidal, and not spindly (A). There are vacuolated cell cords between the macrofollicular structures (B). × 395.



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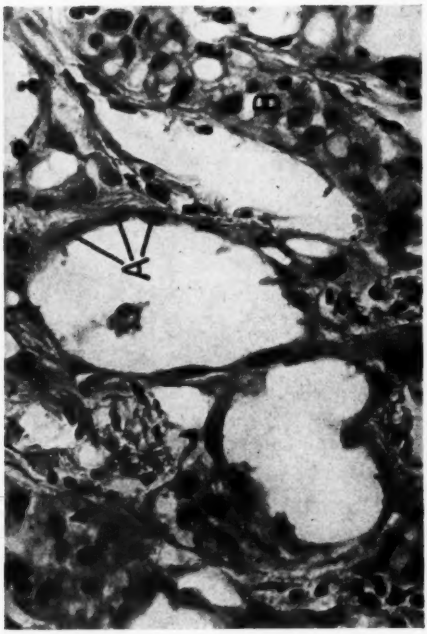

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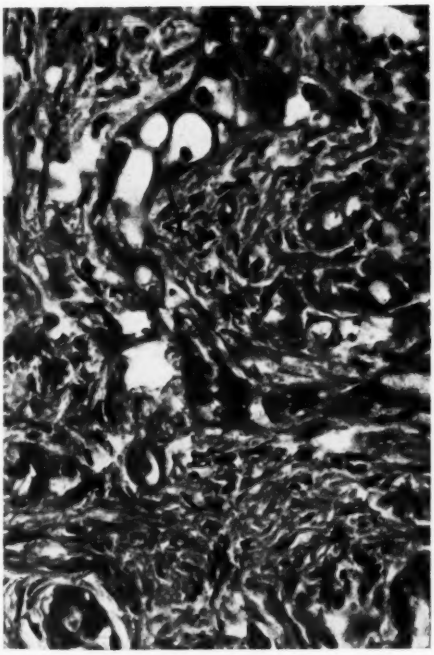

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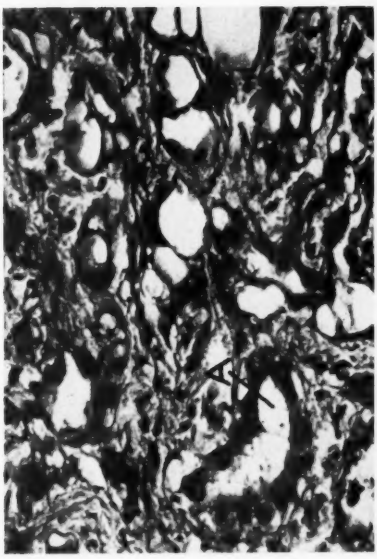

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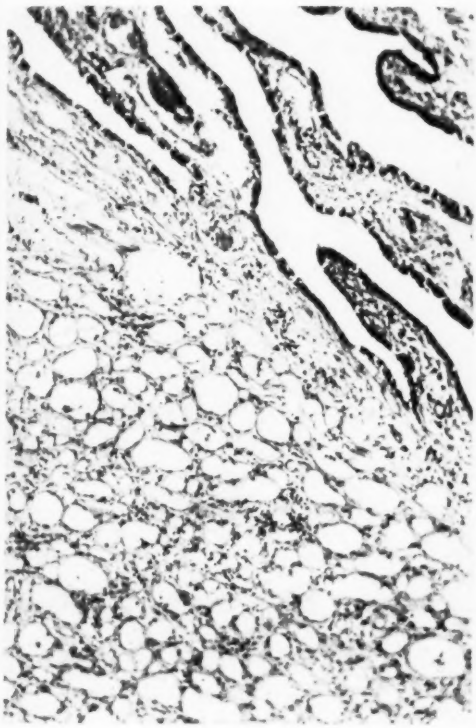
Adenomatoid Tumors of the Genital Tract

PLATE 14

FIG. 9. Acc. 91983, A-36-1427, Neg. no. 77134. The neoplasm present in one of the two cases of involvement of a uterine tube. × 74.

FIG. 10. Acc. 84615, Neg. no. 77131. The reticulum meshwork has a fine to coarse perifollicular arrangement. × 74.

FIG. 11. Acc. 84615, Neg. no. 77130. Smooth muscle bundle inclusions in this instance have an arrangement (A) which is almost myomatous. × 74.



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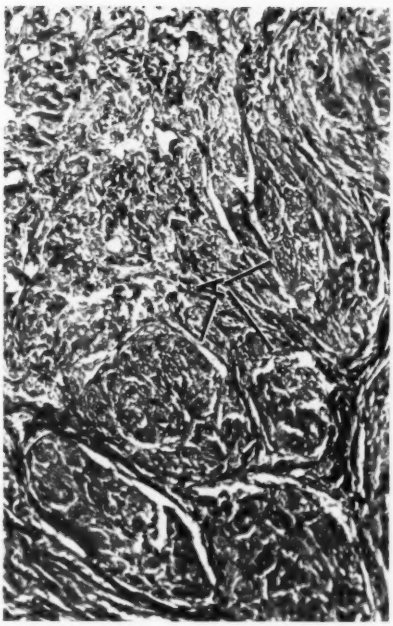

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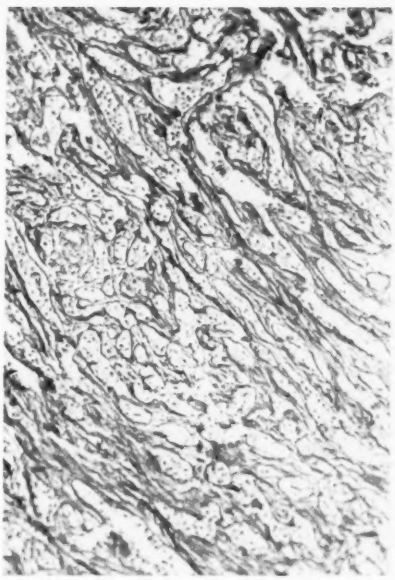

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Adenomatoid Tumors of the Genital Tract

ACCESSORY SPLENIC TISSUE WITHIN THE SCROTUM
Report of a Case *

Harry G. Olken, M.D.
(From the Department of Pathology, Tufts College Medical School, Boston, and the Laboratory of Pathology, Lynn Hospital, Lynn, Mass.)

Accessory splenic tissue is no medical novelty. In fact, it is found so commonly in the course of routine autopsies that Lubarsch[1] stated that accessory spleens should be included in the normal anatomy of the adult. The reported incidence of accessory spleens at necropsy varies from 11 per cent[2] to 35 per cent.[3] The variation apparently depends upon the zeal of the particular investigator and the care with which his search is conducted.

The accessory splenic bodies vary markedly in size and may, at times, be quite numerous. Almost invariably they lie in close proximity to the spleen, being located in the hilum or in one of the surrounding ligaments. More rarely they are associated with one of the neighboring organs, such as pancreas or liver.[4]

Accessory splenic tissue within the scrotum, however, is a distinct oddity. Such an occurrence was first reported in 1913 by Sneath,[5] who described a splenic appendage attached to the upper pole of the left testis of a Negro, 45 years of age. This bulbous appendage was attached to the spleen by a narrow band which passed through the inguinal canal after traversing the peritoneal cavity and joining the spermatic cord. More recently (May, 1943) Emmett and Dreyfuss[6] described a somewhat similar case in which accessory splenic tissue was found within the scrotum of a white man, 47 years old. With their case report these authors included an excellent summary of the meager literature on the subject.

Report of Case

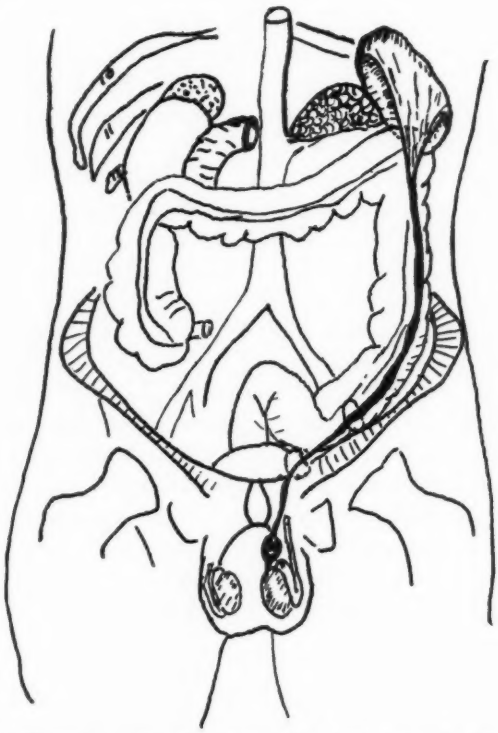
Clinical History. The patient, a white male, 56 years old, was admitted to the Lynn Hospital (case no. 110726) complaining of diffuse abdominal pain and hematemesis. A clear-cut history as to onset and progression of the symptoms was not obtainable as the patient was semicomatose and had been on an extended alcoholic bout. Physical examination revealed a moribund man, with a tender and spastic abdomen. The lungs were clear. A firm, nontender mass was felt within the scrotum, apparently attached to the upper pole of the testis. Temperature was 102° F., and the pulse rate was 140 per minute. On several occasions during the period of hospitalization the patient vomited a coffee-ground fluid.

In spite of therapy the patient died on the second hospital day, with a diagnosis of probable bleeding and ruptured peptic ulcer, or gastric carcinoma, with generalized peritonitis.

* Received for publication, February 15, 1944.

Autopsy Findings

At autopsy (Lynn Hospital autopsy no. A-43-52) an acute, bleeding, duodenal ulcer was found. The ulcer had perforated and had resulted in a generalized fibrinopurulent peritonitis. All of the thoracic and abdominal organs were normally formed with the exception of the spleen, and all showed the effects of the severe infection and associated toxemia.



Text-Fig. 1. Diagram showing the relationship of the spleen and its appendage to the abdominal viscera.

The spleen (weight, 200 gm.) was slightly enlarged. It occupied its regular position in the abdominal cavity but was misshapen. Arising from the anterior aspect was a tapering tail of splenic tissue which continued down along the left lateral wall of the abdomen as a firm cord. This cord was encased in a fibrous capsule and contained a core of brownish splenic tissue. It varied in diameter from 0.3 to 0.5 cm. At the left internal inguinal ring it joined the spermatic cord, passed through the inguinal canal and terminated in the form of a bulbous tumor-like mass measuring 1.8 by 1.0 by 1.0 cm. (Text-Fig. 1). This

lay close to the head of the epididymis and was attached to the tunica albuginea by a broad base (Fig. 1). As it was completely covered by tunica vaginalis, it was not visible until the sac was opened. The cut surface of this bulbous mass resembled normal splenic tissue, being composed of a reddish brown parenchyma surrounded by a dense fibrous capsule (Fig. 2).

A small accessory spleen, 0.8 cm. in diameter, was found within the abdomen close to the hilus of the spleen.

Microscopic Examination

Examination of the tissue mass which lay close to the head of the epididymis showed the typical histologic configuration of a spleen with a fibrous capsule, trabeculae, sinusoids and pulp (Fig. 3). There was a moderate inflammatory hyperplasia of the pulp, a reaction seen also in the abdominal spleen.

Discussion

In the first reported case of a scrotal spleen, Sneath [5] described, more truly, a splenic appendage which lay within the tunica vaginalis testis. In this respect it resembled the case herein reported. Since then other reports have described bands between the spleen and the genital organs, some of these bands consisting of typical splenic tissue.[7,8] That such bands are not always present, however, was shown by Emmett and Dreyfuss.[6] They reviewed 4 cases and added another of their own in which the scrotal spleen was in no way connected with the abdominal organ.

The appearance of this splenic tissue in so distant a place as the scrotum is readily explained on the basis of the close embryologic relationship which exists between the spleen and the urogenital organs. This has been well described and illustrated in previous reports.[5,6] Both the spleen and the testis make their appearance at about the fifth week of fetal life. The spleen appears as a thickening of the layers of splanchnic mesothelium of the dorsal mesentery of the stomach. The testis, arising as an indifferent sex gland from the medial surface of the Wolffian body, comes to lie in front of the primitive kidney on the posterior wall of the abdomen. The two organs are thus brought into close apposition, and fusion of the two is not inconceivable. Under such circumstances the testis, in its descent during the latter weeks of intrauterine life, might readily drag along a tail of developing splenic tissue.

Although accessory spleens usually arouse no great medical curiosity, they may offer an interesting clinical problem. They have been known to produce symptoms by torsion of the pedicle, by causing

intestinal obstruction,[9] or by preventing proper response to splenectomy in such conditions as thrombocytopenic purpura [3] or hemolytic anemia. Accessory spleens may participate in all pathologic processes to which the spleen is heir. Inflammation or hyperplasia in scrotal splenic tissue can produce intense discomfort or pain in this region.[9] Similarly, as a palpable but unexplained mass in the scrotum, it could present a difficult diagnostic problem.

Thus the presence of accessory splenic tissue within the scrotum is not only of academic interest to the embryologist and pathologist, but is also of some importance to the patient and physician as well.

Summary

A case is reported of accessory splenic tissue within the scrotum. Very few similar cases have been reported previously.

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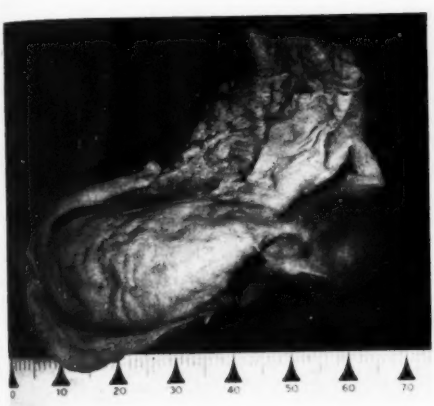
DESCRIPTION OF PLATE

Plate 15

Fig. 1. The tumor is seen adjacent to the head of the epididymis. The fibrous cord at the upper pole of the tumor eventually joins the spermatic cord.

Fig. 2. A cross section of the tumor shows a typical splenic structure with a fibrous capsule, trabeculae and splenic pulp.

Fig. 3. Section of the scrotal tumor showing characteristic splenic histology, with trabeculae, follicles, pulp and a thickened capsule. Hematoxylin and eosin stain. × 95.



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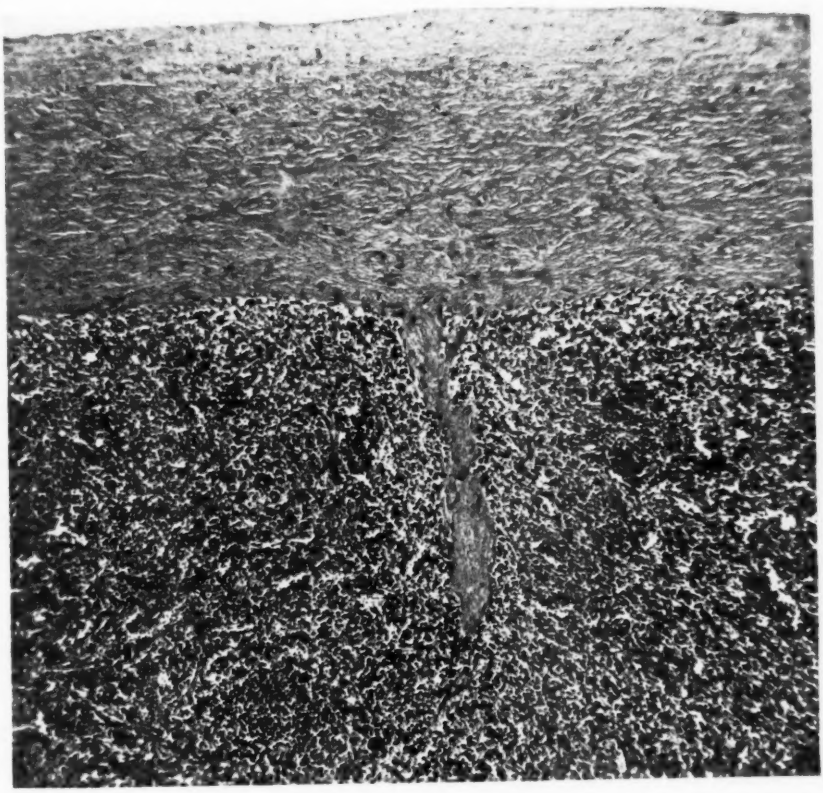

3

Olken Accessory Splenic Tissue within the Scrotum

STUDIES ON THE MOTOR CELLS OF THE SPINAL CORD
III. Position and Extent of Lesions in the Nuclear Pattern of Convalescent and Chronic Poliomyelitis Patients *

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Although the literature on the lesions of poliomyelitis is very extensive, it contains scarcely any data on the exact position and extent of lesions in the spinal cord. Probably one reason for this lack has been disagreement on the arrangement of motor nuclei in the cord; for in the absence of a dependable map of the nuclei one cannot very well say which are affected, and so it would be hardly profitable for anyone to follow a lesion through serial sections. Hence the character of the lesion has received more attention than its form and site.

Yet, if the nuclear pattern were known and so could be used as a frame of reference, it might prove worth while to study the disposition of the lesions. If any tendency to regularity were found in the pathological picture, this would obviously be of significance, enabling us to visualize the process of invasion and recovery and furnishing us with evidence as to the route followed by the virus into the spinal cord.

In two previous communications [1, 2] I have described and confirmed a map of motor-cell distribution in normal human spinal cords; and thus it is now possible to refer lesions to an established pattern, and to state exactly what parts of the pattern have been affected.

Accordingly a number of cords from convalescent and chronic cases of poliomyelitis have been studied with respect to the disposition of the lesions, and are reported on in this paper.

Literature

As remarked at the outset, numerous authors have discussed cellular pathology in poliomyelitis; and they have paid particular attention to the motor cells of the ventral horns, since these are the classical site of lesions. Warburg,[3] in particular, has described the appearance of cells in chronic cases, providing a good bibliography and summary of preceding papers on this topic. But of these, Schwalbe [4] alone has paid any attention to the positions and extent of the lesions; he found that they started centrally in the ventral horns and that marginal cells were

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most likely to survive. Since then, Horányi-Hechst [5] has made a similar report; from a material of 38 cases he found that in the cervical segments the central groups suffer most severely, the dorsolateral less, and ventrolateral still less; while in the lumbosacral region the medial groups suffer more severely than do the lateral. He also found that the 2nd and 3rd lumbar, and 6th, 7th and 8th cervical segments were most frequently and extensively involved, and that, whereas the most rostral and caudal portions of the thoracic region were frequently involved, the intermediate region was rarely affected. Hurst [6] mentioned that an infiltrative process lay immediately adjacent to the central canal in one case, and Peers [7] commented on survival of caudal groups, but even this degree of localization is lacking in most accounts of the lesions.

Material and Methods

The following account concerns cords from 5 human subjects who had suffered from poliomyelitis and subsequently died from other causes. The lapse between onset of the poliomyelitis and death was at least 2 months, and in 1 case was 50 years. To these was added the cord from 1 monkey which had convalesced about 3 months after a severe attack. The human cords, as may be seen from the acknowledgments, were obtained from widely scattered sources and under a variety of circumstances. They had an age-spread of 7 to 61 years, and were all from male subjects.

Complete serial sections were cut from material embedded by the routine paraffin method and mounted *in toto*, excepting every eleventh section which was mounted with its fellows separately in case it were found advisable to study any level with an additional stain. The main series were stained with toluidine blue, and some of the auxiliary series with hematoxylin and eosin.

The sections were studied with a vertical projector by which charts were made after the method described in previous papers of this series, resulting in enlarged tracings each showing cumulative cell distribution in a series of sections. Lesions were determined by defects in the recognized cell pattern at any level, and by asymmetry between the two sides. These charts were made of the nuclear masses supplying the limbs, at short intervals where the pattern seemed normal, but for all sections where lesions arose.

Observations

The individual reports gain in interest and significance by summarizing them in advance of their presentation.

A very definite and consistent trend was found in the localization

of the lesions. The dorsal and medial nuclei were the most frequently attacked and often suffered alone, whereas the lateral and ventral nuclei were less frequently attacked and then only when the dorsal and medial nuclei were also destroyed. When a nucleus was destroyed only in part it was always the dorsal or medial portion that suffered. In other words, the invasion appeared always to radiate from a dorsomedial point.

All degrees of invasion were observed, from those in which there was only a small defect in the most medial or dorsal nuclei (case 70) to those in which all motor nuclei through a whole limb area were destroyed excepting a few cells around the rim of the ventral horn (case 73). Each example added something to the consistent picture of a process that had started dorsomedially and eaten into the lateral cell mass, each showing the process arrested at a different stage. Every lesion, great or small, was roughly fusiform, thrusting most deeply into the nuclear mass at an intermediate level, and less deeply at levels rostral and caudal to this, until it tapered to nothing; this gave the impression that each began from a single point and spread longitudinally as well as transversely.

A widely penetrating lesion did not necessarily have a great caudorostral extent but might be only 1 mm. long (case 108); while a lesion that encroached very little on the nuclear mass might extend through entire segments (case 70); but in most cases the degree of transverse and longitudinal extent was more nearly proportional. Again, a region otherwise denuded of cells might show an almost complete nuclear pattern in a few isolated sections (case 86).

In regard to the levels at which lesions appear there is no regularity apparent in this small series of cases.

The following detailed reports on the individual cords are arranged in order from that of the case showing the least involvement to that showing the most. Each description begins caudally and passes rostrally. Throughout, the term "cell" should be understood as referring to motor cells of the ventral horns only. For nuclear numbers, see Text-Figure 1.

Case 70

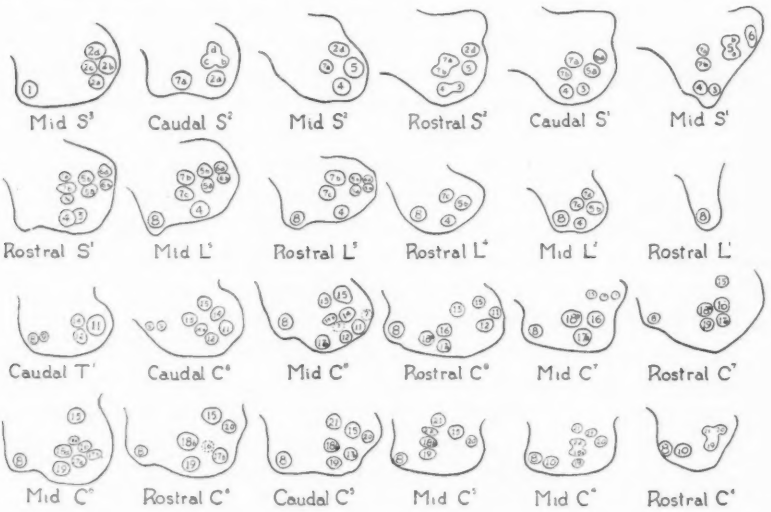
Male, age 61. Cause of death: exsanguination from penetrating gastric ulcer. Poliomyelitis "in childhood." Muscular findings: right psoas definitely smaller than left, muscles of right thigh slightly atrophied anteriorly and medially.

In the lumbosacral region the nuclear pattern was complete and marked; but on the right, nucleus no. 5 and, to a lesser degree, no. 6, were somewhat more sparse from about mid-S1 to about mid-L5. In the cervical region the pattern was poorly marked; at two levels there was a medial defect, slight but quite definite. The exact nuclei involved could not be determined because of the indistinct pattern (Text-Fig. 2).

Involvement of nuclei nos. 5 and 6 confirms the general thesis, especially as these nuclei are very far dorsal in this specimen. That no. 5 should suffer most severely is also typical. Localization of psoas and perhaps quadriceps and abductors in nos. 5 and 6 is a contribution to nuclear identification. The cervical lesions are typical.

Case 108

Male, 30 years of age. Cause of death: subacute bacterial endocarditis. Poliomyelitis at age of 2 years. Muscular findings: equinus deformity of right foot and general muscular atrophy of leg and thigh.



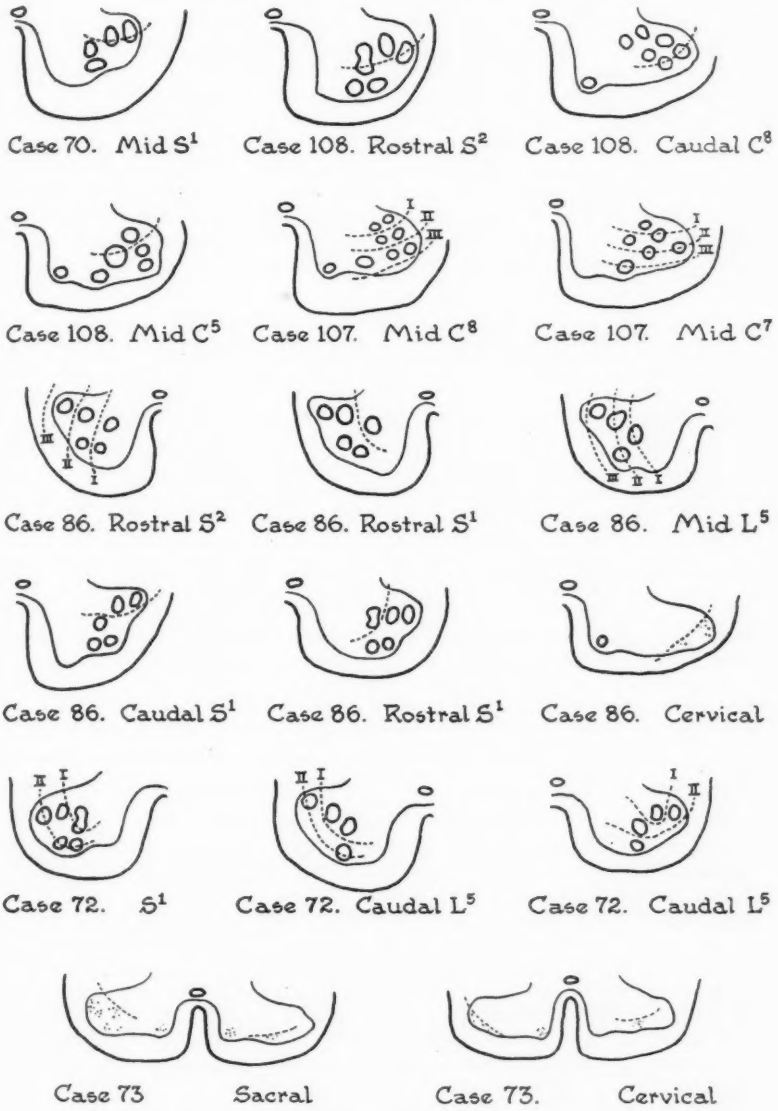
Text-Fig. 1. Diagrams of the ventral cell column cut in transverse section at the levels indicated. (Reproduced by permission from *The American Journal of Anatomy*, 1943, 72, 29–38.)

In the lumbosacral region: on the left, all nuclei were normal; on the right, nos. 3 and 4 were normal, nos. 7 and 6 were present but sparse, no. 5 was lacking excepting scattered groups in the rostral segments, no. 2 was entirely lacking. In the cervical region: on the left, all nuclei were normal; on the right, in caudal C8, there was an almost complete lack of cells for about 1 mm., surviving cells lying at the lateral and dorsal margins of the horn, and at about mid-C_5 medial groups, probably nos. 18 and 19, became sparse though still represented.

These lesions all support the general thesis, except that it is unusual for no. 7 to be spared at all when no. 5 is destroyed. The leg lesions conform very well to the paralytic picture and so make a further contribution to nuclear identification; it has been suspected that nuclei nos. 3 and 4 have to do with the glutei, which are presumably intact in this case, while no. 6 has to do with the iliopsoas, also presumably intact. Survival of some lower leg muscles should account for the equinus and may correspond to the survival of cells in no. 7.

Case 107

Male monkey, age unknown. Cause of death: intentional exsanguination followed by perfusion with a 4 per cent formaldehyde solution. Infection occurred 2 months



Text-Fig. 2. Cross sections through the lesions as described in the text.

Dotted lines represent the extents of lesions; dotted lines designated by Roman numerals represent successive encroachments of a lesion at successive levels. A dotted line passing through a nucleus signifies either that that part of the nucleus is destroyed or that the nucleus as a whole is thinned out.

In the examples from cases 86 and 73 in which outlines of nuclei are not shown, the level, and consequently the nuclear pattern, could not be determined. The dots represent the cells found through a considerable thickness of material.

A few lesions have been omitted because of obvious difficulties in representing them diagrammatically, or because they are duplicated by examples already shown.

and 23 days before death. Muscular findings: lower limbs apparently totally paralyzed; tail, perineum, upper limbs normal and slightly hypertrophied.

In the lumbosacral region all nuclei were destroyed except no. 1 and small caudal portions of nos. 2 and 4. In the cervical region: on the right, all nuclei were normal; on the left, at about mid-C8, all nuclei vanished for a few sections only, beginning with the most medial and ending with the most lateral, and reappearing in the reverse order; and again, about mid-C7, all the nuclei vanished beginning with the mediodorsal, and up to caudal C6 only a few scattered cells could be seen along the ventral boundary, after which all nuclei reappeared abruptly.

All of these lesions confirm the main thesis. The cervical lesions are particularly striking in this case, in view of the hypertrophied arms.

Case 86

Male, age 7, colored. Cause of death: apparently respiratory complications due to poliomyelitis. Infection occurred 2 months and 5 days before death. Muscular findings: stiff neck, paralysis of right arm, weakness of left, apparent involvement of respiratory muscles.

In the lumbosacral region: on the left, no. 2 began weakly and vanished about caudal S2; about rostral S2 nos. 7 and 4 vanished abruptly, followed at brief intervals by nos. 3, 5 and 6—*i.e.*, all nuclei present at that level—and they reappeared in the same order; in rostral S1 no. 7 again vanished for a short distance; finally, in mid-L5 the whole mass faded out in the same order as before—7, 5, 4, 3, 6—only no. 6 reappearing and continuing to the end of the enlargement. On the right, in caudal S1, nos. 5 and 6 faded out, reappearing about 1 mm. more rostrally; in rostral S1 no. 7 faded out briefly; and in caudal L5 the whole mass faded out in the same order as the two left-side examples, and did not reappear. In the cervical region few cells survived; a small group appeared at two levels—in the absence of a nuclear pattern it cannot be said which levels—at the extreme lateral tip of the left horn.

All seven lesions in the lumbosacral region support the general thesis. The surviving groups of cells, rostrally in the left lumbar region, and in the cervical region, offer further support.

Case 72

Male, 54 years old. Cause of death was undetermined; sudden respiratory seizure. Poliomyelitis at 15 years. Muscular findings: severe paralysis of the left leg. Only the lumbar enlargement was available.

On the left side: in caudal S1 nucleus no. 7 faded out, followed in order by no. 5 and parts of nos. 3, 4 and 6, the latter being represented by marginal cells; about rostral S1 the nuclei reappeared in the same order; in caudal L5 no. 5 disappeared, followed by no. 7, and in rostral L5 nos. 4 and 6 also disappeared, all but a few cells on the margin of the horn persisting for 2 or 3 mm. On the right side: in caudal L5 no. 5 disappeared followed by nos. 7 and 6; in rostral L5 no. 6 reappeared transiently; in caudal L4 all cells vanished except a few on the ventral margin of the horn which persisted for 2 or 3 mm.

Three large lesions and the positions of surviving cells all support the general thesis.

Case 73

Male, age 52. Cause of death: sarcoma. Poliomyelitis at 22 years. Muscular findings: paralysis of right arm, leg and erector spinae. Portions of the lumbosacral and cervical regions were available.

In the lumbosacral region: on the right, all nuclei but no. 1 were lacking, though a few cells were found at the ventral margin of the horn; on the left side there

seemed to be a general deficiency of cells, but this could not be confirmed since there were no right-hand nuclei for comparison, and no single nucleus was lacking at any level. In the cervical region: on the right, all nuclei were lacking but no. 8, but a few cells survived at the ventral margin; on the left, more cells had survived, concentrated ventrally, but the pattern was so disrupted that no nuclei could be identified.

The surviving cells confirm the thesis. It is interesting to observe the scattering of cells that have survived, presumably for many years, in an almost entirely denuded and atrophied region. And it is amazing that a person should have survived with motor cells so depleted.

Discussion

The regularity in position of the lesions is as complete as it was unexpected. In all 6 cases, comprising nearly a score of distinct lesions, there is no exception to the rule that cell destruction appears to start dorsomedially and to spread ventrolaterally. To this finding must be added the testimony of the two previous investigators, Schwalbe [4] and Horányi-Hechst,[5] who localized lesions in the cord, testimony which is in exact agreement with the present findings. Horányi-Hechst, in particular, with his 38 cases, adds weight to the conclusions; but his localizations are somewhat rough and generalized and he does not make clear that the ventral and lateral lesions are always accompanied by dorsal and medial lesions, but merely indicates a greater frequency of the latter type; nor does he describe the extent of the lesions. He worked entirely on acute or early convalescent material, which is much more difficult to analyze than is chronic, and had, of course, no reliable or easily available map of the nuclei. Nevertheless, there can be little doubt as to his meanings, and the outstanding thoroughness of his paper in other respects indicates that his findings are perfectly reliable. As to his statistics on the segments most frequently involved, comment will be more appropriate after my larger series of cords with acute lesions has been studied, but in the present series my findings agree with his.

At first sight the uniformity of the findings seems out of keeping with the clinical capriciousness of the disease. Of course, within the limitations hereby introduced there is still room for considerable variation: besides variation in the extent of damage and the number of lesions from subject to subject, the level of the lesions is apparently not restricted, even if certain levels are preferred; a lesion may involve one dorsomedial nucleus in one case and another in another; and its spread may be more ventral or more lateral. At the same time it must be remembered that certain muscles are traditionally susceptible to poliomyelitis, such as the tibialis anticus, opponens pollicis, and deltoid. It has, of course, been argued that the susceptible muscles

are only apparently so, for their paralysis is very obvious and so would be more easily and frequently detected, and this may be true to some extent. But the present findings very definitely indicate that some nuclear groups, and consequently some muscles, are really more apt to be affected than are others. Hence the findings are certainly not in disagreement with the clinical picture of the disease.

This means that an observer has at least a helpful indication in distinguishing muscles paralyzed by destruction of their motor neurons, and thus irretrievable, from those paralyzed or weakened by disuse, spasm, stretching, or other secondary influences, and thus possibly retrievable. For it could be inferred that if certain muscles were spared, those whose nuclei lay more ventrally or laterally were probably also spared, appearances to the contrary; while conversely, if certain muscles are definitely affected, those whose nuclei lay more dorsally or medially would almost certainly be affected also. Likewise, muscles whose nuclei lay between evident zones of total destruction and successful resistance could be watched and treated with appropriate care. In brief, the clinician can build up a clear picture of what is happening in the cord.

To attain these advantages it would, of course, be necessary to determine which nucleus corresponds with each muscle. So far this has been accomplished only fragmentarily, as will be discussed below.

The fact that in many cases a lesion appears to radiate from a single focus is very striking. It indicates that the virus may be transmitted to the cord by one, or a small group, of fibers. More widespread lesions can be accounted for either by more prolonged spread from one focus, or by a greater number of foci. In any case the number need not be very great, for a dozen lesions would quickly overlap to obliterate all motor cells in a limb region. Groups of cells surviving in an otherwise denuded region can be interpreted as lying at the juncture of two focal fields of invasion.

Nucleus-Muscle Relationships

Some evidence is presented on nucleus-muscle relationships, and the foregoing discussion illustrates the need of information in this field. Hence a brief survey of present knowledge of such relationships may not be out of place. Destruction of nerves and study of resultant chromolysis is rarely successful; a number of studies based on this method, notably those of Marinesco [8] and De Neef,[9] have produced contradictory results which, moreover, cannot be reconciled with my map of the motor nuclei; personal experiments of this type have met with little success. Long-standing or recent amputations seldom—

never in the few cases I have seen—show a recognizable reaction. Romanes' [10] study on a specimen with a congenitally deficient limb, and similar work reviewed by him, provide definite but rather generalized information. Cords from patients with poliomyelitis whose muscular picture has been carefully studied are rare, as shown by the extensive survey required to obtain those here discussed.

From the sources referred to it can be accepted confidently that nucleus no. 1 supplies perineal muscles; no. 2, intrinsic muscles of the foot; no. 8, the spinal musculature; and nos. 11 to 15, the hand. Probably nos. 3 and 4 supply the glutei; no. 5, the quadriceps; and no. 6, the iliopsoas; while no. 15 has shown reaction to lesions of the ulnar nerve. Obviously, these localizations can at best be only partly correct, for they leave out many important muscles, including almost the whole arm.

The present findings indicate that no. 6 does supply the iliopsoas, and no. 5 the thigh muscles, and add that no. 7 supplies some lower leg muscles. Confirmatory evidence is offered by the fact that nos. 3 and 4 are frequently spared as are the glutei, while no. 7 is frequently involved as is the tibialis anticus.

The present study illustrates the danger of drawing conclusions from sections taken at only one or two levels in a region. Such sections might well pass through levels that were completely atypical for the region as a whole, showing many cells when the bulk of the region was almost denuded, as in case 86 cervical, or the reverse, as in case 107 mid-C8. If a cord is to be analyzed carefully, numerous or, preferably, serial sections should be taken.

Finally, the occurrence of limited but severe lesions in regions where the muscular picture would not lead one to suspect them is interesting. This was particularly so in the case of the monkey (107), where careful dissection showed the arms not only normal but hypertrophied. Such a condition leads one to suspect that many cases of poliomyelitis occur with involvement of motor cells of the spinal cord and yet without overt paralysis. This agrees with the findings of Howe and Bodian [11] (1942) and furthermore suggests that yet more extensive lesions might occur with no more than a muscular weakness which would not be classed as paralysis. One not infrequently observes supposedly normal persons with awkwardness of gait, posture, or gesture which might well result from such a lesion; and this accords with the prevalence of immune substances in the blood of many supposedly normal adults. This would at least reduce the number of cases occurring with, supposedly, no neural involvement.

The reason for the preferential destruction of dorsomedial nuclei is a matter of vital importance, since it bears directly on the natural history of the disease. But one can hardly theorize on the basis of six subjects. I feel that a greater insight into the question will be obtained when I have completed a large series of cords from acute cases, now in course of preparation.

Summary

The motor nuclei of the limb region were studied in cords from 5 human subjects and 1 monkey convalescent from, or with residual lesions of, poliomyelitis.

All lesions involved the dorsal and medial nuclei first and most severely.

Lesions in general were not diffuse but each appeared to arise from a single focus.

Knowledge of this trend may help the clinician in visualizing what is going on in the cord of a patient; but more satisfactory data on nucleus-muscle relations are needed for this purpose.

Evidence was found as to the functions of certain nuclei.

The findings illustrate the hazard of studying cases of poliomyelitis from single sections, which may give an entirely unrepresentative picture.

Motor cell destruction is found without recognizable paralysis, suggesting nervous involvement in many so-called abortive cases.

The force and conclusiveness of these findings would be greatly increased if the number of cases could be enlarged. If any reader can supply a cord from a convalescent or chronic case of poliomyelitis it would be most gratefully received.

I wish to express my warm appreciation for the very generous cooperation received from many quarters in pursuance of this work. State and Provincial departments of health, departments of pathology, hospital staffs, private doctors, and scientific journals have all aided in canvassing the continent for material. For the specimens used in the present paper I am indebted to: Dr. I. Erb, Sick Childrens' Hospital, Toronto; Dr. E. Linell, Department of Neuropathology, University of Toronto; Dr. E. B. Krumbhaar, University of Pennsylvania; Dr. W. Mathews, Shreveport Charity Hospital, La.; and Dr. R. H. Gourlay, McGill University. The monkey was provided by the kindness of Dr. J. Craigie, of the School of Hygiene of the University of Toronto.

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VISCERAL LESIONS IN POLIOMYELITIS *

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While poliomyelitis is the subject of much research, and many studies on its etiology, its epidemiology, and its immunologic and serologic aspects are on record, recent gross and histologic studies of organs other than the brain and spinal cord are singularly lacking. An exception is the recent report of Dublin and Larson [1] upon the results of 12 post-mortem examinations made during the epidemic of 1940 in Pierce County, Washington. They found, in addition to the lesions in the brain and spinal cord, lymphoid hyperplasia of the intestinal mucosa and mesenteric nodes, acute myocarditis twice, and bronchopneumonia in three instances, with abscess formation in one. Apparently one of these instances of myocarditis had been previously reported by Larson [2] (1941). Hemorrhagic pulmonary edema was outstanding in three cases. The liver regularly disclosed some degree of hydropic change and, in some instances, fatty degeneration.

This study is based on post-mortem examinations of 17 patients who died of clinically diagnosed poliomyelitis during the recent Chicago epidemic. The duration of the disease varied from 3 to 8 days. The diagnosis of bulbar and spinal poliomyelitis was made in 13 cases. Bulbar poliomyelitis was diagnosed four times, and in one of these encephalitis was also recognized clinically. There were 12 children under 14 years of age, 2 adolescents, 16 and 17 years old, and 3 adults, 20, 23 and 28 years old. All patients had received various amounts of either convalescent human serum or pooled normal human serum. Six patients received sulfadiazine. A respirator was used for 4 patients.

The outstanding changes encountered at autopsy were as follows: The hearts were dilated and often soft and flabby. The mural and valvular endocardium was smooth. The papillary muscles and chordae tendineae were flattened. The myocardium invariably was pinkish gray or brownish gray and of boiled appearance with loss of its normal architecture. Petechial hemorrhages were often encountered in the endocardium and epicardium. In one instance they were abundant and covered practically the entire visceral pericardium.

The lungs grossly disclosed several findings. In ten instances marked edema and acute hyperemia were encountered. Slight bronchopneumonia was detected three times and severe bronchopneumonia twice. In

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six lungs in which either edema and hyperemia or no gross change was encountered, significant lesions were discovered on microscopic examination. The bronchi and trachea showed no lesion in these instances. In some of these latter patients, attending physicians had diagnosed a mucous plug in the bronchus. It was surprising that such a mucous plug was actually encountered at necropsy only once. Moderate emphysema was found twice in children who, because of difficulty in breathing, had been placed in a Drinker respirator. Edema and hyperemia also were found in these lungs. Only the lungs of 1 patient were free from pathologic change.

Cloudy swelling of varying degree was invariably present in the liver and in the kidneys. In the latter, however, passive hyperemia was the outstanding finding.

The intestinal tract disclosed most commonly a marked hyperplasia of the lymph follicles and of Peyer's patches. There was also, in these instances, a hyperplasia of the peritoneal lymph nodes. Occasionally, hyperplasia of the Peyer's patches was so severe as to resemble that seen in the stage of medullary swelling of typhoid fever. It may be noteworthy, however, that the hyperplasia was not observed in 3 patients, the oldest in this series, who were 20, 23 and 28 years old, respectively.

Cerebrospinal lesions may be summarized only. Twelve patients disclosed inflammatory lesions in the brain itself in addition to the lesions in the medulla oblongata and spinal cord. The regions surrounding the ventricles were most commonly involved. These changes were particularly common in the vicinity of the fourth ventricle. The cerebellum was also frequently involved. The most outstanding site was the dentate nucleus. The spinal cord disclosed grossly recognizable, minute and larger foci of hemorrhage within the gray matter. These lesions were encountered always, but not exclusively, in its anterior horn. Often the posterior portions were also involved but usually to a lesser degree. The changes were marked in the cervical and often in the upper thoracic cord, and became less pronounced or were absent in the lower thoracic segment, but again were more prominent in the lumbar region.

Microscopic examination of the myocardium disclosed myocarditis in ten instances. In two the inflammatory changes were very marked and diffuse, in six they were more or less localized, and in two hearts the changes were only slight. In the first two hearts the changes were so severe that there seemed to be a massive extravasation of leukocytes. Many polymorphonuclear leukocytes were encountered and also lymphocytes. The proportions of these two cell types varied markedly

in the various sections. Red blood corpuscles also were present in the inflammatory exudate. Many heart muscle fibers were compressed by the exudate and appeared thinned out, while others were the seat of cloudy swelling. There was no evidence of necrosis. In the six instances in which the inflammatory exudate was localized, it was seemingly confined to the interstitial tissue. This exudate consisted of lymphocytes and only a few polymorphonuclear leukocytes. Endothelial leukocytes were rarely encountered. Both the right and left ventricles were involved. Often the inflammatory changes were most marked in the vicinity of epicardial hemorrhages.

The aortas, which grossly had disclosed no noteworthy changes, were the seat of microscopic alterations in three instances. There was an edema-like material seen in the media separating the elastic lamellae and sometimes interrupting their course. Often this material had a pinkish, smudgy, fibrinoid appearance. Here and there an occasional lymphocyte could be made out. Neither the intima nor adventitia showed any change.

In the lungs, the lesions encountered grossly could easily be verified microscopically. Thus, edema and hyperemia were very often seen, and bronchopneumonia in varying degrees was observed five times; in three it was very slight. However, in six additional instances definite interstitial pneumonia could be demonstrated. It was noted that the smaller bronchi in these instances disclosed the presence of lymphocytes and of polymorphonuclear leukocytes within the submucosa, whereas the lining cells of the mucosa were intact. The lumina of these bronchi did not contain an appreciable number of inflammatory cells. The only noteworthy change in the mucosa was a thickening of the basal membrane. It could be demonstrated that the inflammatory cells from the submucosa of the smaller bronchi extended either within or along minute vessels into the alveolar septa, which often were crowded with lymphocytes, polymorphonuclear leukocytes and red blood corpuscles. Here and there some of these inflammatory cells extended into the adjacent alveoli. Occasionally a thin eosinophilic, homogeneous material could be made out lining the inner wall of the neighboring alveoli. The larger bronchi and the trachea also had a thickened basal membrane of the mucosa and, sometimes, varying numbers of inflammatory cells throughout their walls. The lumina rarely contained an accumulation of mucus. As stated before, a mucous plug was encountered grossly only once. The lining epithelial cells of the trachea and larger and smaller bronchi were carefully examined for inclusion bodies. In not a single instance, however, were inclusion bodies encountered.

The solitary follicles and Peyer's patches in the lower ileum and cecum were sometimes enormously hyperplastic. The hyperplasia involved the germinal centers. There was, however, no evidence of necrosis in these areas. The adjacent regions of the intestinal tract showed no inflammatory changes whatsoever. The spleen and mesenteric lymph nodes also disclosed follicular hyperplasia with conspicuous germinal centers. In the midst of some of the latter, foci of necrosis were discernible. No other change could be detected. In the remaining viscera there were no noteworthy histologic lesions.

The microscopic changes in the brain and spinal cord will be enumerated only, since there are many reports on record describing these changes and this study contributes no new details. As noted grossly, the more severe lesions in the cerebrum and cerebellum were found in the vicinity of the ventricles, particularly about the fourth ventricle. The dentate nucleus was frequently involved. Many ganglion cells disclosed degenerative changes with absent nuclei and with Nissl's granules obscured. Lymphocytes and occasionally—in some instances, however, more pronounced—polymorphonuclear leukocytes were encountered perivascularly. Here and there small accumulations of proliferated microglial nuclei could be seen. In the spinal cord the changes in general were not confined to the anterior portions of the gray matter, though they were most conspicuous in these areas. The changes consisted of marked hyperemia, minute foci of extravasation of red blood corpuscles, and perivascular infiltrations of lymphocytes, mainly, and a few polymorphonuclear leukocytes. Hemorrhage never constituted a predominating feature. In the more severe examples the inflammatory cells were found diffusely throughout the gray matter. Here and there ganglion cells, evidently necrotic, were found in the midst of the inflammatory exudate. Endothelial leukocytes, though in general not numerous, seemed to be relatively more frequent in these areas. Often the regions surrounding the central canal were the seat of an inflammatory reaction. Although the white matter of the cord was rarely involved, small infiltrations of lymphocytes occasionally were observed. The meninges also contained inflammatory cells more or less confined to the perivascular areas, particularly in the more severe instances.

Comment

Aside from the known lesions in the brain and spinal cord, the more outstanding changes encountered in these 17 cases of poliomyelitis were myocarditis and interstitial pneumonia.

Myocarditis was found ten times. It must be stressed that in some instances myocarditis was recognized in the first few sections exam-

ined, but in the majority a number of blocks had to be examined before evidence of myocarditis was found. From this study it seems evident, and it apparently also holds true for many other infectious diseases, that myocarditis will be encountered frequently if the myocardium is examined histologically with the specific purpose of either ruling out or establishing the presence of inflammatory alterations.

Since myocarditis is known to occur in instances of pneumonia [3] or as a result of sulfa drug medication,[4] the question arises as to whether or not the myocarditis in poliomyelitis may be related to these two factors. However, the clinical records disclosed that 4 of the 10 patients did not receive sulfa drugs, though the remaining 6 did receive sulfadiazine. Only 4 of the patients showed at necropsy evidence of pneumonia. All patients were treated clinically with either pooled serum or serum taken from patients who had recovered from poliomyelitis. It does not seem likely that the myocarditis signifies a so-called serum reaction, since an exudative reaction following administration of homologous human serum is allegedly very rare.[5] None of the patients showed any clinical signs or symptoms which possibly could be the result of an abnormal serum reaction. It should be pointed out that the patient who had the most severe myocarditis had received pooled normal serum and not convalescent serum. In this series there was no relationship between the presence or absence of myocarditis and the type of poliomyelitis, whether principally bulbar or spinal.

An instance of polioencephalomyelitis associated with optic neuritis and myocarditis was reported as early as 1913 by Hertz, Johnson and Depree.[6] However, this was a clinical observation, and no autopsy was performed to verify the clinical diagnosis of myocarditis. Wile and I [7] recorded myocarditis in poliomyelitis in six of seven hearts which were specifically examined histologically for myocarditis. Peale and Lucchesi [8] found myocarditis of some degree on histologic examination in seven of nine hearts of patients with poliomyelitis. Larson [2] stated that since neither bronchopneumonia nor any other source of infection was found in his patient as the cause of the myocarditis, it may be theorized that the myocardial involvement was produced by the virus of poliomyelitis.

The sudden death of some of these children can easily be explained by the myocarditis. Hassin [9] described a child with poliomyelitis, who presented a clinical picture of Landry's paralysis with microscopic inflammatory changes within the muscles. The sudden death of this child was attributed to involvement of the myocardium.

Another interesting finding in this series was the presence of an interstitial pneumonia. It was observed that the inflammatory exudate

spread from the submucosa of the smaller bronchi into the peribronchial tissues and thence into the alveolar septa. The inflammatory cells were lymphocytes and polymorphonuclear leukocytes, sometimes the former being more numerous. This interstitial involvement of the lung was often found in conjunction with a severe hyperemia. It is noteworthy that this type of pneumonia was encountered in those instances in which there was much cyanosis clinically, and when the attending physician had expected a mucous plug within the trachea or bronchi. This pneumonia resembled so-called atypical pneumonia. However, the inflammatory cells were not principally monocytes as in atypical pneumonia. Though no inclusion bodies were found anywhere in the lungs, it is possible that a virus may have caused this pneumonia. It might be of interest in future cases to conduct virus studies with material taken from the lungs of patients who die from poliomyelitis.

Hyperplasia of the intestinal lymph follicles and Peyer's patches has often been observed and originally suggested the gastrointestinal tract as the portal of entry.[10] However, the hyperplasia of the solitary lymph follicles and of the abdominal lymph nodes differed in no way from that seen in many acute infectious diseases in childhood. Microscopically there was no evidence of acute inflammatory change in the vicinity of the lymph follicles. There were, however, occasional small foci of necrosis of germinal centers. It is also noteworthy that the older patients in this series did not have this lymphoid hyperplasia.

Summary

The findings at necropsy of 17 patients dying from poliomyelitis are recorded. The changes in brain and spinal cord were not unusual and are given only cursory mention. In ten instances myocarditis was found. It was detected only on microscopic examination and varied greatly in extent and severity. Often it was noted in the vicinity of minute or larger epicardial or endocardial petechial hemorrhages. Myocarditis was apparently in no way related to pneumonia or to therapeutic measures. The sudden death of some of these patients may be attributed to the myocarditis. Interstitial pneumonia was encountered six times. It is possible that the pulmonary lesions were caused by a virus. Bronchopneumonia was present five times. Hyperplasia of the lymph follicles and Peyer's patches, although almost constant in children, is not an important feature and is not characteristic of poliomyelitis.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 16

FIG. 1. Heart with inflammatory cells principally in the interstitial tissue. Most of the cells are lymphocytes but a few polymorphonuclear leukocytes are present also. Iron-hematoxylin and eosin preparation. × 150.

FIG. 2. Severe degeneration of myocardial fibers with diffuse infiltration of inflammatory cells, mainly polymorphonuclear leukocytes. Iron-hematoxylin and eosin preparation. × 130.

FIG. 3. Myocardium. Inflammatory cells are located principally in the interstitial tissue. The inflammatory cells are both lymphocytes and polymorphonuclear leukocytes. Iron-hematoxylin and eosin preparation. × 80.

FIG. 4. Heart with heavy infiltration of polymorphonuclear leukocytes and lymphocytes. Iron-hematoxylin and eosin preparation. × 130.

FIG. 5. A field similar to that shown in Figure 4. Iron-hematoxylin and eosin preparation. × 200.

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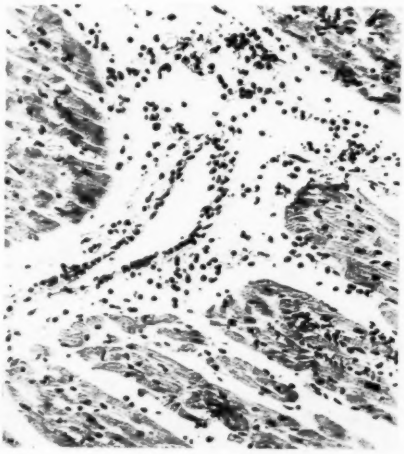

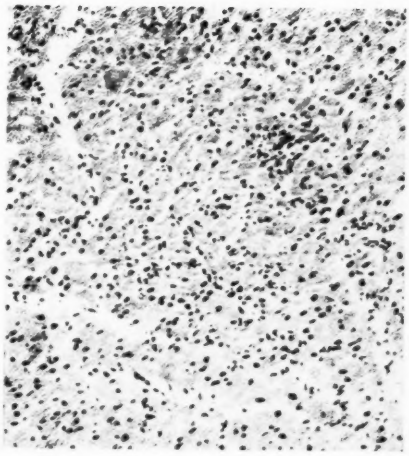

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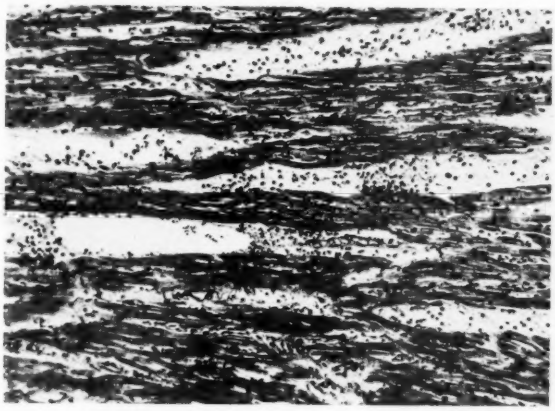

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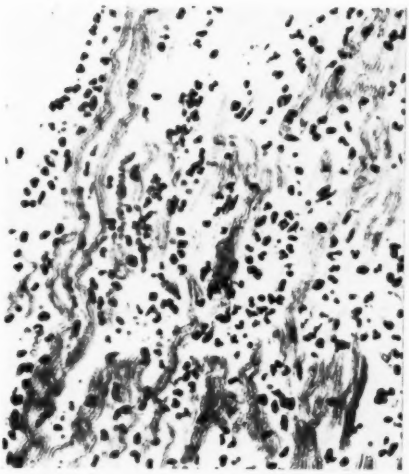


5

Saphir

Visceral Lesions in Poliomyelitis

Plate 17

Fig. 6. Aorta, showing edema-like material separating the elastic lamellae and the presence of few inflammatory cells. Iron-hematoxylin and eosin preparation. × 120.

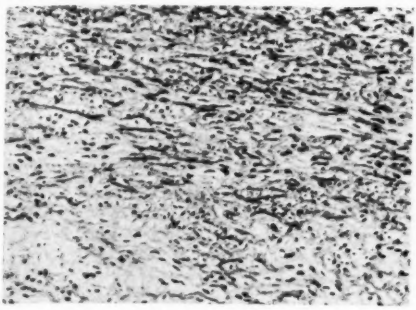
Fig. 7. A field similar to that shown in Figure 6. Iron-hematoxylin and eosin preparation. × 180.

Fig. 8. Trachea, showing hyperemia and the presence of lymphocytes and a few polymorphonuclear leukocytes within the submucosa. Iron-hematoxylin and eosin preparation. × 140.

Fig. 9. Small bronchus, showing infiltration of the submucosa principally with polymorphonuclear leukocytes, and extension of the inflammatory cells between the muscle fibers. Iron-hematoxylin and eosin preparation. × 150.

Fig. 10. Interstitial pneumonia. Lymphocytes and a few polymorphonuclear leukocytes are present within the septa, while the alveoli are empty. Giemsa preparation. × 110.

Fig. 11. A field similar to that shown in Figure 10. Giemsa preparation. × 180.



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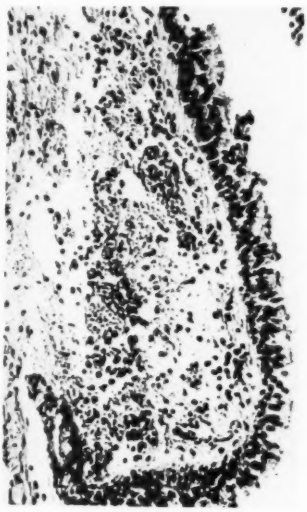

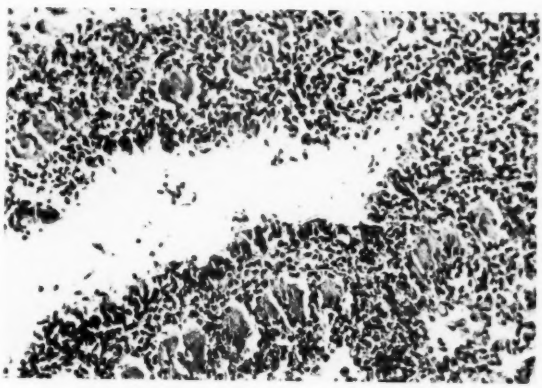

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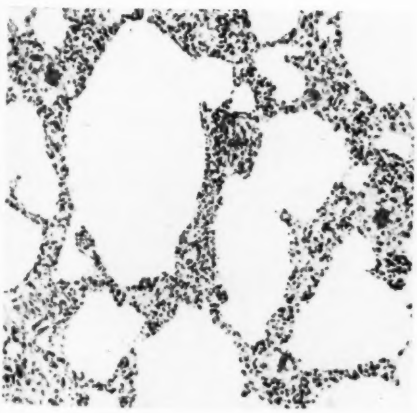

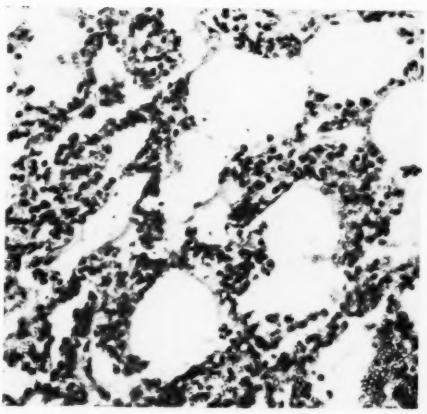

11

Saphir

Visceral Lesions in Poliomyelitis

GASTRIC ULCER IN SWINE*

H. C. H. KERNKAMP, D.V.M.
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Ulcers, that from their gross and microscopic appearance are strikingly similar to the ulcers of the stomach in man, have been observed in the stomachs of swine. A report of our findings on gastric ulcer in swine is submitted.

The cases of stomach ulcer which I have studied were all found in connection with a necropsy service on animals. The series from which they were collected includes a total of 754 swine. Eighteen (2.38 per cent) of these pigs had one or more typical ulcers in the stomach. In general, the gross morphology of the ulcer was that of a rounded, circumscribed excavation in the mucous membrane. The floor of the ulcer was flattened and below the surface of the surrounding mucosa. In 2 cases the floor extended into the muscle coats and the serosa over this area was thickened. The walls were usually steep. The rim or border overhung the wall in 1 case. A zone of inflammation surrounded the lesion in most cases, and, in 2, bleeding from the lesion was very evident. Microscopic examination shows that the mucous membrane stops at the ulcer crater in most of the cases. Where the muscle coat was involved, the muscle seemed to be retracted and dense fibrous tissue invaded the area. The floor was covered with granulation tissue.

A single or solitary ulcer occurred in 10 cases and 2 or more (2 to 15) ulcers were present in the other 8 cases. In 5 of the cases in which a solitary ulcer was present, the lesion was situated in the pyloric gland region. The ulcer was situated in the fundic gland region in 2 cases and in the cardiac gland region in 2. No record is available for 1 case. For the most part, the ulcers were on the greater curvature of the stomach. The largest ulcer measured 6 cm. in diameter. When more than a single ulcer was found, their particular location was usually not recorded. However, in one instance, 4 ulcers were present in the fundus, and in another, 6 were in the pyloric region.

Unfortunately, the exact age of our animals is not known, but a reasonably accurate approximation of the age can be made in most instances. The youngest pig with gastric ulcer was a Duroc-Jersey male between 6 and 7 weeks old. In this pig, there were 4 ulcers in the fundic gland region and each measured about 1.5 cm. in diameter. The state of nutrition in this animal was very poor. It was thin, dehydrated and weak. The history on the group from which this pig

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was chosen as representative revealed that a nutritional or iron-deficiency anemia had been prevalent about 2 or 3 weeks previously. A diagnosis of post-anemic cachexia with secondary gastric ulcers was made. A history of what probably was nutritional anemia was obtained on 4 other cases with gastric ulcer. These pigs, however, were between 10 and 14 weeks of age. Bronchopneumonia was considered to be the principal cause of the illness or death in 5 pigs that showed stomach ulcers at necropsy. In none of these cases was the illness ascribed to the gastric lesion. In 2 animals, the ulcers appeared to be healed or healing. The age of these pigs was estimated to be from 5 to 8 months. Hog cholera was the cause of the illness or death in 6 cases. In addition to the excavating ulcer in 1 of the latter, there were present a few ulcers of the "button" variety more commonly seen in this disease when ulceration occurs. These pigs were all more or less acutely sick and came from herds in which others were sick or dead. The youngest pig in this group was about 60 days of age and the oldest about 7 months. In 2, the chief gross pathologic process accountable for their clinical condition was an extensive diphtheritic and necrotic colitis (generally described as infectious enteritis in veterinary medical literature). One was a female between 4 and 5 months of age which weighed only 30 lbs.; the other was a female of 11 months that weighed 180 lbs. The gastric ulcers in these 2 cases presented evidence of advanced healing, the mucosa dipping down into the crater and covering part of the floor whereas the inflammation in the lower bowel was more acute.

Comment

The occurrence of ulcers in the stomachs of swine, which from their morphologic characteristics are not unlike the gastric or "peptic" ulcers in man, has been observed on 18 occasions. In not a single instance was their presence suspected from any signs or symptoms displayed by these animals. If a free incision of the stomach had not been made and the mucosal surface everted and freed of ingesta, several of these ulcers would have been missed. This disease in swine, based upon the series studied, shows an incidence of 2.38 per cent. It is to be noted that at least 98 per cent of the animals comprising the series were pathologic cases submitted to our necropsy service for the express purpose of ascertaining the cause or nature of the disease responsible for their condition. Even though the viscera of millions of swine are handled by veterinarians in the meat inspection service of the Federal Government each year (46,520,000 hogs slaughtered under Federal inspection in 1941 [1]), no information on the incidence of gastric ulcer in the general swine population is available. The reason

for this is that the stomachs are not incised and the mucosal surface not examined at the "bench" unless some obvious lesion on the serosa warrants the investigation.

The group of pigs with gastric ulcers is much too small to establish the incidence as to sex. Eight were males. That all were pigs less than 1 year of age may be of some significance in respect to the cause. In this connection, I wish to point out that in age the pigs in the entire series (754 swine) ranged between stillborn and nearly 5 years old. The greatest number, however, were between 5 and 11 months of age. Typical excavated ulcers of the gastric mucosa were found in a pig scarcely more than 1 month of age, and also in a few others that were less than 4 months of age. The presence of an ulcer in such young animals suggests that there may be a causal relationship to the occurrence of nutritional anemia. Nutritional anemia is not an uncommon disturbance of suckling pigs that are born in the late winter and early spring in this part of the country. No satisfactory explanation for the specific and definite cause of these ulcers in swine is forthcoming at this time.

REFERENCE

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AN OVINE MONSTROSITY

(CORMO-MELODIDYMI DIPYGUS BIDORSUALIS) *

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Since teratology has been placed on an embryological basis, much of the mystery and superstition concerning the development of monsters has been eliminated. By scientific study of terata, it is shown that anomalies are the result of irregularities arising at any stage of the developmental period.

According to Arey: [1]

"The incidence of major malformations in the newborn [human] is about 1:165, the ratio is higher in aborted fetuses, while the inclusion of minor anomalies would raise the frequency for both groups.

"Through the perversion of developmental processes, embryology and pathology find a common meeting ground; indeed, teratogenesis may be characterized as pathological embryology."

Stockard [2] believes that developmental inhibition or arrest is the single causal factor in most abnormal development, including twinning. He inhibited the developmental process by lowering the temperature or reducing the oxygen supply, the resulting type of deformity being dependent solely on the precise moment when the interruption occurred.

Double monsters, according to present theories, may originate from two ova which are united, or may be produced by division of a single ovum.

DESCRIPTION OF THE SPECIMEN

The monstrosity was sired by a Shropshire ram, and its dam was a grade Shropshire ewe, 3 years old. Parturition was of long duration but accomplished without assistance. The gestation period was approximately 150 days, and all organs were apparently fully developed. Death occurred near or at the time of birth.

According to Gurlt's classification of monstrosities as presented by Fleming,[3] the specimen is designated as "Cormo-melodidymi dipygus bidorsualis." It consisted of two fetuses of approximately equal size forming a symmetrical monster having one head, and four thoracic and four pelvic limbs. This monocephalian monstrosity was joined at the ventral surface from the umbilicus cephalad, and had the liver, spleen, pancreas, stomach, part of the intestine, lungs and heart in common. Complete separation of the equal conjoined twins occurred posterior to

* Received for publication, April 3, 1944.

the umbilicus, while the union of the vertebrae became complete at the axis to form one atlas which articulated with the single head.

Anatomical Detail

The Skeleton. Deep dissection and, finally, maceration were necessary to demonstrate the one complete skull which articulated with the single atlas. The axes and the third cervical vertebrae were paired, but united to their fellows of the opposite side by their transverse processes. The vertebral formula of each lamb, counting the single atlas with both, was C. 7, T. 13, L. 6, S. 4, Cy. 15.

Two sterna were present, actually assuming a right and left position to form a portion of the lateral walls of the common thoracic cavity. Thirteen pairs of ribs were present, with seven sternal and six asternal.

Complete skeletal development was shown by the four thoracic and four pelvic limbs.

Digestive and Respiratory Systems. Both the hard palate and the soft palate were cleft to a severe degree. Figure 3 shows them to be only slightly developed. Often cleft palate is associated with hare lip, but there was no evidence of this condition. The tongue was thickened dorsoventrally so that its dorsal surface fitted into the cleft of the palate.

Not only did the oral and nasal cavities communicate, but also it was found that the respiratory and digestive tracts were developed as a common tube extending from the oral and nasal cavities to a point midway between the base of the heart and the diaphragm. This esophago-tracheal tube with a single lumen contained plates of cartilage in its dorsal and ventral walls; no complete rings were developed. A horizontal membrane divided the lumen of the incompletely developed larynx into dorsal and ventral parts. The posterior displacement of the larynx to a point ventral to the third and fourth cervical vertebrae was unusual. The esophago-tracheal tube terminated near the center of the diaphragm in four bronchial apertures and three esophageal openings. The right bronchi supplied the two lungs of the left lamb similarly. A central digestive aperture entered the centrally located omasum, while an aperture on each side of this central opening entered bilateral abomasa.

From the left abomasum, the intestine coiled to the left, occupying mainly the abdominal cavity of the left twin until it terminated posterior to the cecum in two branches. Each branch of the intestine continued as the normally arranged colon to the rectum of its respective lamb. Each anus was perforate.

A single large liver extended across the abdominal cavity in relation to the single complete diaphragm. The liver received a large portal vein and two umbilical veins. Inside the liver, the portal and umbilical veins united to form a venous sinus, from which the blood entered the ductus venosus.

A single spleen was observed in the left lamb and one pancreas was found in the right lamb.

Urogenital System. The urinary system was normal and complete for each individual. Both lambs were females, normal genitalia being present in the left lamb, but incomplete development only in the right. The right ovary, uterine tube and the uterus of this lamb presented normal development, but the left uterine tube and horn were absent. The left ovary was found in the broad ligament, having no tubal connection with the uterus.

Circulatory System. Two umbilical veins passed from the common umbilicus to the liver where they anastomosed with each other and formed a venous sinus by confluence with the single portal vein. From the venous sinus, the blood passed through the ductus venosus to the very large posterior vena cava. The vena cava deviated to the side of the left lamb but entered the right atrium. Further dissection revealed a small vein on the right side extending from the iliac vein (and receiving the renal, uterine and lumbar tributaries) to the junction of the right jugular vein and the anterior vena cava.

A single heart supplied both individuals, but the pulmonary artery and aorta were so developed that contraction of either ventricle would force blood to both lambs. The right and left ventricles were of almost equal size. Persistence of the foramen ovale was noted.

The accompanying diagram (Text-Fig. 1) illustrates the peculiar arrangement of the arterial system in the cardiac region. The pulmonary artery turns around the aorta, gives off branches to supply the lungs of both lambs, and continues posteriorly as an aorta for the right lamb. It did not give off an anterior mesenteric artery. The right brachial artery branches from the pulmonary artery. An anastomosing vessel connects the arch of the aorta with the arch of the pulmonary artery.

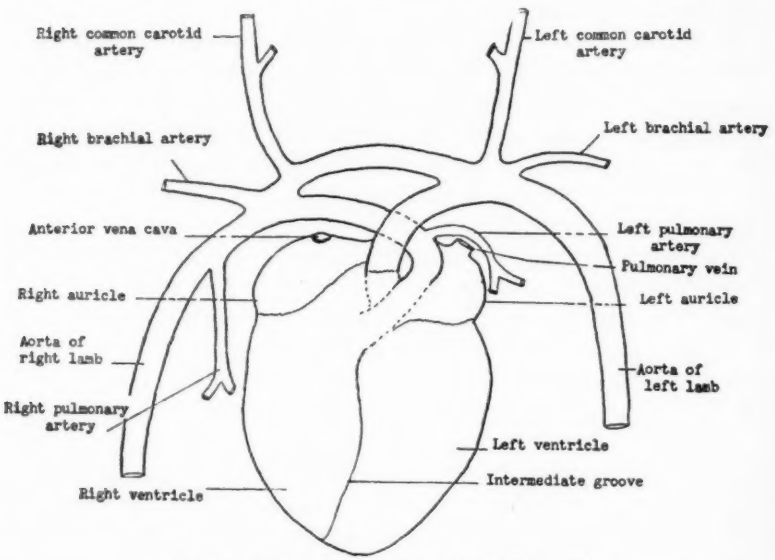
The true aorta arising from the left ventricle gave off coronary arteries and a brachiocephalic trunk, and continued posteriorly in the left lamb in the usual manner.

Four umbilical arteries were noted; two from the external iliac arteries of each twin.

Nervous System. A dual nervous system existed posterior to the

bifurcation of the spinal cord at the second cervical vertebra. A single spinal cord entered the atlas and continued anteriorly to the single brain.

Monsters commonly die at birth due to anomalies which interfere with normal postpartum body functions. In this instance, death may



Text-Fig. 1. Diagram of heart and arterial branches.

have been due to collapse of the esophago-tracheal tube since the tracheal rings were incompletely developed, or to the malformed blood-vascular system which was so arranged as to supply a prenatal circulation but was inadequate for postnatal circulation of blood through the lungs.

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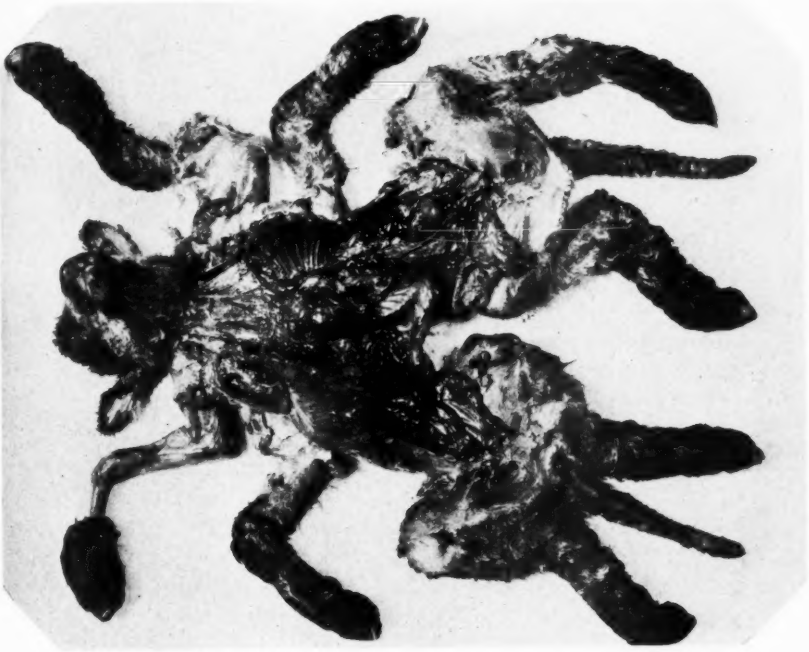
DESCRIPTION OF PLATES

PLATE 18

FIG. 1. Ovine cormo-melodidymi dipygus bidorsualis. Dorsal view.

FIG. 2. Ovine cormo-melodidymi dipygus bidorsualis. Ventral view.



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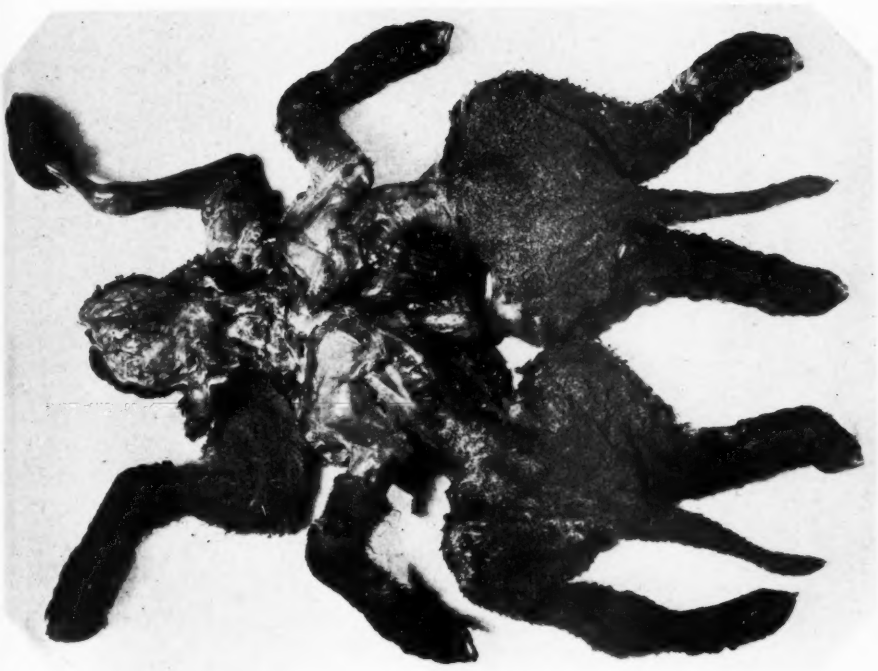

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Goss and Cole Ovine Double Monster

PLATE 19

FIG. 3. Cleft palate and dissected cardiac region.

3

Goss and Cole Ovine Double Monster

EXPERIMENTAL SILICOSIS PRODUCED WITH THE ASH FROM HUMAN SILICOTIC LUNGS *

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The pathologic effects on human lungs of fine silica particles, inhaled in industries where silica hazards exist, are well known. What happens to the silica particles in the body and whether or not they are inactivated for further silicotic reactions apparently has not been determined.

It is now generally accepted that the fine crystalline silica (SiO_2) particle is the toxic agent and that the rate of fibrous reaction which it stimulates depends primarily on its solution in the form of colloidal silicic acid. The freer it is from contamination and the smaller the size of the particles, the more promptly the tissues react to it, and the more rapid and extensive is the silicosis which results. It is known further that the fibrosis of silicosis does not cease when the dust inhalations are stopped but that the process may continue for many years without the stimulation of fresh particles. Mixtures of silica with other dusts such as carbon, iron and aluminum affect the toxicity of silica and modify the severity of, or prevent, tissue responses. When silicotic lungs are analyzed chemically a large portion of the residue is made up of silicates, but so far it is not possible to tell whether the silica was changed in the tissues or whether it was originally inhaled as a mixed dust in approximately the same proportions as those recovered in the chemical extracts. This report deals with the results of injecting the chemically recovered ash of silicotic lungs into experimental animals as second hosts.

For some years, one of us (Taylor) has been making chemical analyses of lungs sent to the laboratory for the diagnosis or exclusion of silicosis. We have not depended upon chemical data alone. We have made gross and microscopic examinations, supplemented by incinerated sections, and have supported our conclusions with chemical data whenever possible.

There exists a considerable divergence of opinion concerning the value of chemical analyses in the diagnosis of silicosis. King and Belt [1] reviewed the subject thoroughly and Belt, Irwin and King [2] reported a series of analyses in which they found as much SiO_2 in lungs of nonsilicotic miners as they found in some of those with massive silicofibrosis. McNally [3] considered that anything over 0.2 per cent indi-

* Received for publication, April 6, 1944.

cated excessive exposure to silica although he cited exceptions to this rule in several of his cases. Sweany, Porsche and Douglass [4] considered anything over 0.2 per cent to be abnormal in the lungs. They found that lymph nodes sometimes contained 5 per cent without a record of abnormal exposure. Gardner and Redlin [5] made analyses of 150 lungs for silica content: 58 were from persons with no known exposures to silica, 20 were from subjects with histories of exposure but with no evidence of silicosis, and 72 were from persons who had both a history of exposure and classical lesions. In 32 instances there was no correlation between the content of silica and the lesions present. They concluded that there could be no exact correlation between free silica and pathologic reactions; that free silica may be high and its irritating influence counteracted by inhibiting minerals; and that the true relative values may be lowered by an excess of newly formed tissues in the silicotic lung. We would agree, in general, with this statement although our results so far have coincided with the findings of Sladden [6] in that lungs which have advanced silicofibrosis yield constantly more than 1 per cent of silica in dried lung.

There are three precautions that must be observed in the extraction of the ash of silicotic lungs if the results are to be consistent with the degree of dusting that has taken place. Since the silica particles are partly concentrated in the lymph nodes (Belt, Irwin and King [2]) and since the tissues may be unevenly diluted by exudative processes, it is important that whole lungs, as nearly as possible, be used for the recovery of the dust. Only the lowest temperature consistent with reasonable speed of destruction of the organic matter may be employed. Otherwise the physical state of the particles may be altered and with it the physiologic activity (Nagelschmidt and King [7]). Finally, the ash may be extracted only with dilute acid (1.0 N HCl) and for the minimum time necessary for removal of iron and phosphate deposits that tend to cement the particles together as well as to interfere in the determination of the free silica (Taylor [8]). It is also helpful, when the two lungs differ in the pathologic processes present, to determine the silica present in each lung so that they may be compared on the basis of the 47/53 ratio of normal left and right lung weights.

Since the residues of our chemical extracts were small in amount we decided to test them by the injection methods along lines used by Gye and Purdy, Gardner and Cummings, and Miller and Sayers. In 1922, Gye and Purdy [9] demonstrated the toxicity of colloidal silica when injected subcutaneously, intraperitoneally and intravenously into guinea-pigs and rabbits. They found that large daily doses of from

30 to 32 mg. caused death in rabbits in from 2 to 4 days, and that smaller doses injected into rabbits at weekly intervals produced cirrhosis of the liver. Gardner and Cummings,[10] in 1933, developed an injection test for the study of the effects of dust particles, based upon repeated intravenous injections of small doses suspended in normal salt solution. Miller and Sayers,[11] in 1934, used an intraperitoneal technic for testing tissue reactions to dusts of unknown toxicity. They classified the reactions as inert, when the particles provoked a transitory reaction which later disappeared; absorptive, when insoluble dusts produced a minimal amount of inflammation in which the particles were phagocytized and remained in the tissues without an increase in the reaction as time went on; and proliferative, when the dusts contained enough silica, either alone or in association with other dusts, to cause progressive proliferation resulting in the production of fibrous nodules.

Experiments

The general plan of the experiments provided for tests by animal injection of four samples of ash recovered chemically, and a control series in which pure crystalline silica was injected. The cases were selected to include one in which the insoluble dust was low in total silicates and without free silica, two cases in which mixed dusts containing free silica were recovered, and one case from which silicates containing excessive amounts of free silica had been obtained.

In each group three rabbits were given intravenous injections on alternate days of a 1 per cent suspension of the respective ash and three guinea-pigs received injections of 2.5 cc. of a 1 per cent suspension intraperitoneally. As the experiments proceeded, some slight variations in the amounts used became necessary. The silica control group was arbitrarily called group III and will be discussed first.

Control Group III

Rabbits. One rabbit received 6 intravenous injections of crystalline silica on alternate days and died on the 13th day. Another rabbit received 8 injections and died on the 17th day immediately after the last injection. The findings in these two rabbits were limited to nodular thickenings at the sites of injection along the ear veins, to subintimal infiltration in the veins and to accumulations of phagocytes in the liver, sinuses and spleen.

The third rabbit survived 8 injections in the ear veins and lived for 23 months. Grossly, the ear veins presented bead-like nodules, the pleura showed minute black spots, the spleen and kidneys were prac-

tically negative, and the liver showed subcapsular depressed scars and presented the typical picture of cirrhosis. The deep wrinkling of the capsule was present uniformly over the liver save for the spigelian lobe which was replaced by yellow fibrous tissue.

Microscopically, the pulmonary alveoli contained many black-dust phagocytes which tended to collect in the perivascular and peribronchial lymph nodes. Some of the pulmonary veins were thickened and their walls infiltrated with hyaline connective tissue, the meshes of which contained silica phagocytes. Occasional vessels had nodular thickenings in their perivascular zones made up of agglomerations of phagocytes filled with minute silica crystals. In several instances the lymphoid tissue was displaced by central nests of phagocytes. The liver was cirrhotic. The periportal zones were increased in size, thickened, devoid of liver cells and showed hyperplasia of the bile ducts. There were nodular zones made up of fibrous tissue which contained collections of phagocytes. The spleen contained nodules of phagocytes with giant cells and in some instances the centers were necrotic. The kidneys showed a moderate degree of diffuse cortical fibrosis. There were nodules in the ear veins at the sites of injection, composed of collections of subintimal phagocytes filled with particles. The nodules were large and almost obliterated the vascular lumina.

Incinerated sections of the liver showed diffusely distributed agglomerations of silica particles in the fibrous areas. In the ear veins and spleen the agglomerations were much more abundant and more closely arranged.

Guinea-Pigs. Of the three guinea-pigs that received the intraperitoneal injection of 1 per cent silica suspension, one died after the third dose. Post-mortem examination showed small nodules in the muscle at the sites of injection, in the mesentery, omentum, between the intestinal loops and under the liver. The second and third guinea-pigs died at 6 and 18 months after the intraperitoneal injections from obstruction of the bowels due to peritoneal adhesions. They presented similar gross and microscopic changes. The peritoneal lesions were large, necrotic, partially calcified and contained great numbers of multinucleated foreign body giant cells. The spleens showed hyperplasia of the germ centers and collections of silica phagocytes surrounding the germ centers. In one of the animals the splenic veins were filled with crystalline particles as well as some fine, brown, particulate material. Throughout the liver there were nodular collections of phagocytes but no cirrhosis. Special stains for fibrous connective tissue showed that the nodules had formed their own stroma. The lungs of

both animals contained alveolar phagocytes filled with black pigment, probably due to inhaled pigment from the air. The perivascular lymphoid tissue contained some collections of phagocytes filled with black pigment, and several small perivascular lymph nodes contained typical silica tubercles with collagenous nodules suggesting the yarn-ball-like arrangement seen in human cases of silicosis.

Summary of Control Groups. All of the rabbits in the control series showed perivascular phagocytes and the progressive type of silica nodules along the ear veins and in the liver and spleen. The rabbit that lived 23 months showed advanced cirrhosis of the liver. The guinea-pigs that received peritoneal injections showed areas of necrosis, interstitial adhesions, and calcified nodules in the liver, spleen and lymph nodes. The silicotic nodules produced their own collagenous stroma.

Experimental Group I

Group I animals were injected with the ash from a patient who died with bronchogenic carcinoma. The patient, H. G. S., age 53, had been a laborer in and around coal mines for many years. During the 2 years preceding his death, he had become short of breath and easily fatigued. He attributed his condition to the inhalation of dust and entered suit against the company that employed him. X-ray findings were all against silicosis and consisted of massive consolidation, more marked on the left side. At autopsy, the pathologic diagnoses were primary bronchogenic carcinoma of left lung; secondary carcinoma of pleura, pericardium, chest wall, liver, right lung and peribronchial lymph nodes.

Chemical Analysis. The left lung weighed 850 gm. and contained 0.83 mg. of silica per gm. of dried tissue. It was not further analyzed. The weight of the right lung was 940 gm. It contained 0.505 gm. of ash, of which 0.097 gm. were silica. The silica was all in the form of silicates; no free silica was found. As ordinarily expressed, there was 0.79 mg. of silica per gm. of dried tissue, or 0.079 per cent.

Three rabbits and three guinea-pigs were injected as described for control group III. All animals lived throughout the 23 months of the experiment. The rabbits were negative, and the only lesions found in the guinea-pigs which were injected intraperitoneally were collections of phagocytes and foreign body giant cells beneath the peritoneum, filled with brown pigment, and a few similar collections of cells in the spleen. There were no evidences of toxic action, no silica nodules and no fibrosis. The results in this group were typical of the "absorptive" reaction of Miller and Sayers.[11]

Experimental Group II

The second group of animals was injected with the ash of a case of silicotuberculosis.* The patient, J. H., age 70, had been employed for many years in a marble yard. The physical findings had been dullness at both bases, more marked on the right; vesicular sounds in the upper portions, and râles over the dull areas of both lungs. Pathologically, the gross examination of the lungs revealed dense, gray-black scarring of the upper portions of the lower lobes and lower portions of the upper lobes, many small, black, rubbery nodules throughout the remaining portions of the lungs and shaggy adhesions on the pleural surfaces. Sections contained many yarn-ball silicotic nodules, active tubercles and areas of dense fibrosis. Between the fibrous areas there were emphysematous spaces and air sacs filled with pigment phagocytes. Pathologic diagnoses were silicotuberculosis, emphysema, regeneration of pulmonary alveoli and chronic adhesive pleuritis.

Chemical Analysis. The weight of the two lungs, as received in formalin, was 1200 gm. They contained 6.210 gm. of acid-insoluble ash, of which 4.543 gm. were silica. If the right and left lungs be assigned 53 and 47 per cent respectively of the total lung tissue, then the silica per lung was 2.408 and 2.135 gm. respectively. Of this, 60 per cent was combined (silicates) and 40 per cent was free silica. Stated in the commonly used terms, the total silica amounted to 24.2 mg. per gm. of dried tissue, or 2.42 per cent, and the free silica was 9.7 mg. per gm., or 0.97 per cent.

Three rabbits were injected in the ear veins with 2 cc. of a 1 per cent suspension of ash on alternate days for 3 doses and with 2.5 cc. of a 1.25 per cent suspension for 4 doses. All rabbits lived for the entire 23 months of the experiment, when they were sacrificed. Grossly, there were hard nodules along the ear veins at the sites of injection and no other lesions. Microscopically, the changes were identical in the three animals and consisted of collections of dust cells in rosettes in the liver sinusoids and at the borders of the periportal tissues. There were similar, but somewhat larger, collections of dust cells in the splenic pulp and germ centers. The lungs were negative.

Three guinea-pigs were given 3 doses of 2 cc. each of 1 per cent suspensions at intervals of 2 days. One died before lesions appeared and 2 lived 23 months until the end of the experiment. In the gross, the latter both showed a few white, subperitoneal patches. Their livers and spleens contained many minute, grayish, pebbly spots, and their

* Contributed by Dr. Ivan Brown, Reading, Pa.

lungs presented small, blackish spots due to inhaled dust. Microscopically the subperitoneal nodules were made up of large collections of dust phagocytes situated in the fat. There was a feeble attempt at reticulation and encapsulation, and many giant cells. The liver and spleen showed collections of gray phagocytes in the sinusoids and in the pulp.

Summary of Group II Experiments. In spite of the rather high percentage of silicates and the presence of free silica, the results in all of the group II animals were rather weak examples of the absorptive reactions of Miller and Sayers.[11] Apparently the silicates or other components of the extract protected the tissue from the usual toxic effects of the free silica.

Experimental Group IV

The group IV experiments were made with lung ash of a case of silicotuberculosis and pneumonia. The patient, G. S., had been employed for many years in a coal mine as a motorman hauling coal cars in the mine. The tracks required constant sanding and the air he breathed was admittedly very dusty. He was a man beyond middle life who had suffered for many months from shortness of breath, fatigue and general poor health. His death was due to pneumonia and followed an acute illness of about 3 weeks. The lungs were brought in from a neighboring hospital.

The left lung weighed 775 gm. The pleural surfaces were covered with shaggy fibrous adhesions and in part with acute fibrinous exudate. The consistency was tough, fibrous and boggy. On section, there were many small, hard, gray-black nodules from 2 to 4 mm. in diameter and many large areas of fibrous thickening. In the upper, posterior portion of the left lower lobe there was a diffuse, acutely consolidated, portion. At the hilus there were several large, blackened lymph glands containing calcified gray nodules. Microscopically, some of the nodules presented the typical yarn-ball patterns of silicosis while others had caseous centers and were recognizable tubercles. The diffuse consolidated area was one of unresolved pneumonia with healing by organization and fibroblastic repair. Tuberculosis of the lymph nodes was proved microscopically.

The right lung weighed 2040 gm. The pleura was covered with a fresh fibrinous membrane. All three lobes were massively consolidated by lobar pneumonia. In addition to the pneumonia, the surface was studded with pinhead-sized silicotic nodules which were gray and rubbery. The pigment appeared much paler than in the left lung due to dilution with the acute pneumonic exudate. The hilus nodes resembled those on the left. Microscopically, all of the gross lesions were verified.

Incinerated sections from both lungs left an ash which was brownish gray, partly amorphous and party crystalline. Throughout all specimens there were abundant, highly refractive, heat-resistant metallic particles. Application of 1 per cent hydrochloric acid overnight removed the brown material and left the insoluble crystalline silica and amorphous silicates behind. The pathologic diagnoses were nodular silicosis, emphysema, pigment cell interstitial pneumonitis of both lungs, silicosis and tuberculosis of peribronchial nodes, bronchopneumonia, healed conglomerate tuberculosis and organizing pneumonia in the left lung, and lobar pneumonia with organization in the right lung.

Chemical Analysis. The left lung weighed 775 gm. and contained 2.968 gm. of acid-insoluble ash of which 1.375 gm. was silica. Of the latter, 72 per cent was in the form of silicates and 28 per cent was present as free silica. Expressed in the usual manner, there were 11.45 mg. of total silica per gm. of dried tissue, or 1.145 per cent. The corresponding figures for free silica were 3.2 mg. and 0.32 per cent.

The weight of the right lung was 2040 gm. It contained 3.276 gm. of ash and of this 1.611 gm., or 49.2 per cent, was silica. In the customary terms this was 5.7 mg. per gm. of dried tissue, or 0.57 per cent. The ratio of free to combined silica was not determined because previous experience had shown that significant differences were not to be expected from the samples of ash from a pair of lungs.

At once a discrepancy is seen in the silica of the right and left lungs when expressed as milligrams per gram of dried tissue, the left having almost exactly twice the concentration of the right. The explanation is found in the different amounts of acute exudate in the two lungs as indicated by the weights. On drying, the exudate yielded a residue similar in weight to that of normal tissue. The dry weight of the lung was thus much increased. The ash, on the contrary, undoubtedly represented material that had been inhaled before the onset of pneumonia and in quantities in proportion to the weights of the normal lungs.

If the weights of the normal lungs are taken as 360 and 410 gm. respectively, then the left lung is 47 per cent and the right is 53 per cent of the total tissue. The amounts of silica in the two lungs should be in the same ratio. Actually the ratio for the silica found in these lungs is 46:54. The weight of the right lung is about five times the normal. The figure for silica in milligrams per gram of dried tissue is therefore to be multiplied by five to indicate its true significance and becomes 28.5 mg. per gm., or 2.85 per cent. In the same way, the figure for silica of the left lung must be multiplied by 2.15, giving 24.6 mg. per gm., or 2.46 per cent. These are in satisfactory agreement. It is

from such considerations that we favor reporting silica per lung rather than per gram of dried tissue. In none of the lungs involved in this paper was the weight normal.

Rabbits. Three rabbits were injected in the ear veins on alternate days with 2 cc. of a 1 per cent suspension of the residue. One rabbit died during the ninth injection, 22 days after the first dose. Dust cells were found in groups in the liver sinusoids and in the venous spaces of the spleen. There was no fibrosis. Another rabbit received 8 doses in the ear vein and 4 doses intraperitoneally after the ear veins were closed. The animal died 6 months later of peritonitis and pneumonia. In the gross, the effects of silica were seen in large areas of necrosis and organizing abscesses in the abdominal walls. Microscopically, the silicotic nature of the abscesses was proved and incinerated sections showed much highly refractive crystalline material in the necrotic zones. The sections of the organs showed an extremely acute serous exudate with amyloid infiltration of the spleen and renal glomeruli. No amyloid could be demonstrated in the liver sinusoids, even with special stains. The only nodular silicotic lesions were along the ear veins and around the abdominal abscesses. The third rabbit received 9 doses in the ear vein and lived until the end of the experiment. Grossly, the ear veins had beaded nodules. The lungs had several blackened areas from air inhalation. The liver was in an advanced state of cirrhosis with multiple gray nodules and fibrous portions entirely devoid of hepatic tissue. The spleen was grossly negative. The lymph nodes were enlarged and partially replaced by gray nodules. Microscopically, the nodules of the ear veins, spleen and lymph nodes were made up of collections of phagocytes and their silica content was proved by incineration. The cirrhosis of the liver was extensive and the amount of periportal connective tissue greatly increased. There was proliferation or approximation of bile ducts and the fibrosed bands contained occasional nodules suggesting nodular silicosis.

Incineration proved the presence of silica particles in the cirrhotic areas although the number of particles was small in comparison to the extensive fibrosis.

Guinea-Pigs. All three of the original guinea-pigs in group IV, placed together in the same cage, were lost. As there was some of the suspension remaining, two other guinea-pigs were given single doses of 2.5 cc. intraperitoneally, and sacrificed at the end of 3 months. Grossly, they both showed yellowish white nodules at the sites of injection and in the omentum and lesser peritoneum. No lesions were found in the lungs. The Kupffer cells of the livers showed slight proliferation. There were early nodular collections in the spleens and lymph nodes. The

peritoneal lesions had the appearance of early progressive silicotic nodules.

Summary of Group IV Experiments. The only rabbit injected intravenously which lived throughout the experiment developed cirrhosis of the liver, and all of the animals injected intraperitoneally produced nodules of the progressive type described by Miller and Sayers.[11]

Experimental Group V

The experiments in group V were made with suspensions of lung ash from a case of massive silicosis in which there were a few recognizable healed tubercles. The patient, G. H., age 35, colored, had been employed as a castings cleaner for 11 years in a rolling mill and foundry. For 2 years he had had a cough, had become easily fatigued, and had lost weight. For several months he had been bed-ridden and under treatment for "pulmonary tuberculosis."

Left Lung. The pleura was thickened and covered with old fibrous adhesions. On section the lung was dark, slaty red and the consistency was resilient. The posterior, upper and central portions of the upper and lower lobes were solid and air-free. The lower anterior margin of the upper lobe and about one-fourth of the lower lobe contained air. The color of the air-containing portions was red-brown in contrast to the slaty red-gray of the solid parts. There were no cavities. The peribronchial nodes were enlarged and filled with black pigment and white granular nodules.

Right Lung. The pleura was covered with adhesions. All three lobes were consolidated and air-free except the margins of the basal portions. The appearance was essentially the same as in the left lung. Microscopically, no air sacs or alveolar walls remained in the solid portions. Cellular areas containing masses of phagocytes alternated with irregular islands of collagenous, practically nucleus-free, connective tissue. The collagenous zones were nonvascular. In the mucosa of the bronchioles there were occasional miliary tubercles. Large sections, almost an inch square, were taken in which no air sacs were present. In the peribronchial nodes there were numerous typical yarn-ball silicotic nodules, with no active tubercles.

Incineration showed much particulate crystalline matter between the collagenous masses with fewer particles in the collagenous masses themselves. Pathologic diagnoses were advanced massive silicosis, active peribronchial miliary tuberculosis, chronic adhesive pleuritis.

Chemical Analysis. The left lung weighed 1025 gm. It contained 5.680 gm. of ash and of this 4.266 gm., or 75.1 per cent, were total silica. This latter was made up of 73 per cent of free silica and 27 per

cent of combined or silicate silica. As ordinarily reported there were 26.8 mg. of total silica per gm. of dried tissue, or 2.68 per cent. The free silica was 19.5 mg. per gm., or 1.95 per cent.

The right lung weighed 1100 gm. and contained 5.959 gm. of acid-insoluble ash of which 5.002 gm. were total silica. This was made up of 63 per cent of free silica and 37 per cent of combined (silicate) silica. In the dried tissue there were 29.7 mg. per gm., or 2.97 per cent, of total silica and 18.8 mg. per gm., or 1.88 per cent, of free silica. These figures are again deceptively low because of exudate in the lung. Free silica and ash were higher in these lungs than in any others in our series. Injection experiments were made as in the previous groups.

Rabbits. One rabbit received 9 doses of 2 cc. each of a 1 per cent suspension of the extract and died on the 47th day with pneumonia. The organs and surfaces were negative save for silica beading along the ear veins. Microscopically, there were small silica tubercles in the germ centers of the spleen and nests of silica phagocytes in the periportal areas of the liver. The periportal connective tissues were slightly increased in amount. The second rabbit died 6 months after injection. Grossly, the ears were thickened and fibrous, there was a pronounced cirrhosis of the liver and the spleen was enlarged and roughened. Microscopically, the perivascular lymphoid tissue was absent and replaced by fibrous thickening of the adventitia. Occasionally the adventitial thickenings formed small nodules with a few enclosed phagocytes filled with crystalline particles. The spleen contained many silicotic tubercles. Some were in the germ centers and some were in the pulp. Many of them showed a newly formed fibrous stroma. The liver showed advanced cirrhosis which was identical microscopically with that found in the silica controls. There was much fibrous replacement by wide bands and a few collections of phagocytes filled with crystalline particles in the bands. The bile ducts were compressed and apparently isolated in the newly formed connective tissue. The kidneys showed diffuse interstitial fibrous hyperplasia with tubular distortion and compression. The glomeruli did not seem to be affected. The remaining rabbit died during the fourth injection.

Guinea-Pigs. The guinea-pigs in this series each received 3 intraperitoneal doses of 2.5 cc. of a 2 per cent suspension of the lung extract. In one the pleura was mottled, the spleen was enlarged and showed nodules on the capsule. The liver was filled with miliary nodules and had a calcified plaque beneath the capsule. The diaphragm and parietal peritoneum were covered with white nodules. The intestines were adherent to the parietal wall and there were soft, partially calcified, granulomatous masses in the adhesions. The omentum was rolled up

and small, gritty, silicotic abscess foci were distributed along the lower border of the stomach. The intestinal loops were adherent to each other and the mesenteric nodes were enlarged and contained white spots. Microscopically, the lungs contained some well developed perivascular silicotic nodules which replaced the areas usually occupied by lymphoid tissues. The nodules were sometimes larger than the vessels. The liver showed fibrosis in some places and collections of dust cells with giant cells in others. The nodules produced their own collagenous stroma. The spleen was filled with compact silicotic nodules. The granulomas of the parietal wall and between the intestinal loops were typical of those produced in the controls with pure silica. The lymph nodes were replaced by masses of phagocytes with areas of necrosis, and several minute collagenous nodules were present. The adventitia of the vessels of the adhesions were greatly thickened and sometimes necrotic. In places the media was encroached upon and a type of medial sclerosis produced. The findings in the second guinea-pig were practically the same as those of the first. The third guinea-pig died too early in the experiment to show changes.

Summary of Group V Experiments. Of the six animals in the experiment only one rabbit and two guinea-pigs lived for 6 months or more. In all of these, extensive silicotic lesions identical with those in the silicotic control group were produced.

Summary and Discussion

Experiments were conducted by injecting into rabbits and guinea-pigs chemical ash from four sets of lungs sent to the laboratory for analysis and the results controlled with a series injected with suspensions of pure silica. The ash was selected as the representative substance because it contained silica and silicates in approximately the same proportion as they were recovered from the lungs. Suspensions of similar concentration and similar quantities of the respective ashes were used in all injections. The animals in the control group presented the typical lesions described by Gye and Purdy,[9] Miller and Sayers,[11] Gardner and Cummings,[10] and others, and included nodules of the lungs, spleen, lymph nodes, peritoneum and blood vessel walls. In one rabbit injected intravenously, which lived for the 23 months of the experiment, there was a well developed cirrhosis of the liver. Of the group I series, which received lung ash from a case of bronchogenic carcinoma in which 0.079 per cent of the ash was total silica without free silica, all lived throughout the experiment and presented mild lesions of the type designated by Miller and Sayers as the "absorptive type." Group II animals received injections of lung ash from a case

of silicotuberculosis in a marble worker that contained 2.42 per cent total silica and 0.97 per cent free silica. Five of the six animals lived throughout the experiment and all showed pronounced absorptive lesions without fibrosis. The results in this series were not as anticipated and indicated that the silicates and other contaminating dusts protected the animals from the toxic action of the silica. In group IV the animals were injected with suspensions of lung ash from a case of silicotuberculosis that contained 1.145 per cent total silica, of which 0.32 per cent was free silica. Progressive granulomatous lesions were obtained in the peritoneum, lymph nodes and spleens. The only rabbit that lived for the duration of the experiment developed cirrhosis of the liver comparable to that found in the silica control. The animals of group V were inoculated with suspensions of ash from a case of massive silicosis in which the ash contained 2.68 per cent total silicates and 1.95 per cent free silica. One rabbit and two guinea-pigs lived 6 months or more and in all typical silicotic nodules of the lungs, liver, spleen and lymph nodes were produced. The rabbit presented advanced cirrhosis of the liver and the guinea-pigs had calcified granulomas of the peritoneum.

Three of the findings require additional discussion; *viz.*, cirrhosis of the liver, nodules of the lungs of guinea-pigs which received only intraperitoneal injections, and adventitial lesions in the walls of vessels associated with granulomas.

Gye and Purdy [9] described cirrhosis due to repeated sublethal injections of colloidal silica and Gardner and Cummings [10] used cirrhosis as a positive criterion in testing unknown substances for silica content. It was to be expected that extensive cirrhosis would be found in the silica control group and in the group V animals in which 73 per cent of the ash was free silica. It was more surprising to find cirrhosis very pronounced in the group IV rabbit where the ash contained only 28 per cent free silica. Incinerated sections showed relatively few crystals in the fibrous areas. Fifteen rabbits were used in the combined experiments and in only three instances was cirrhosis found. These were in the silica control group III and in test groups IV and V. Since other rabbits that lived 6 months or more showed silicotic liver nodules but no cirrhosis, the probability of an extraneous cause was not great.

The guinea-pigs injected intraperitoneally with pure silica and with the suspension of ash from the case of massive silicosis showed in the lungs well developed perivascular nodules composed of agglomerations of silica phagocytes. In explanation of these findings the work of Ungar and Wilson [12] is of interest. They produced chemical peritonitis in one set of animals, marked the phagocytes of the exudate *in vitro*,

washed the cells and reinjected them into a second series. They found that regardless of the site of injection (some injections were made directly into the portal vein) the marked phagocytes concentrated in the lungs. It seems likely that the silica in suspension, injected into the peritoneal cavity, taken up locally and found regularly in the livers and spleens, also reached the lungs in sufficient amount to produce the perivascular nodules.

Some of the perivascular lesions in the margins of silicotic granulomas of the peritoneum were most striking, while the vessels of the same animal taken at a distance from the granulomas appeared normal. The affected vessels had very thick walls. The intimal coats were normal. The muscular coats were thickened unevenly owing to irregular replacements of the muscle cells by a waxy type of connective tissue. The adventitial coats were very wide and fused with the stroma of the granulomas. They too presented a myxomatous appearance and were generally infiltrated with phagocytes having one or more nuclei. Both arteries and veins were affected. The vascular changes were comparable to many of those seen in advanced silicosis of human lungs.

Conclusions

1. Experimental silicotic lesions were produced in animals with injections of suspensions of ash recovered chemically from the lungs of cases of human silicosis.

2. The lung extracts were made from whole lungs and care was used to prevent overheating and overacidifying so that the silica was recovered in the same condition, as nearly as possible, as it existed in the lungs. Silica extracted in this way had not lost its toxic activity during its sojourn in bodily tissues.

3. Just as had been found in human pneumoconiosis, the activity of the ash appeared to depend upon the amount of free silica present and upon the modifying influences of accompanying substances in the residue.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

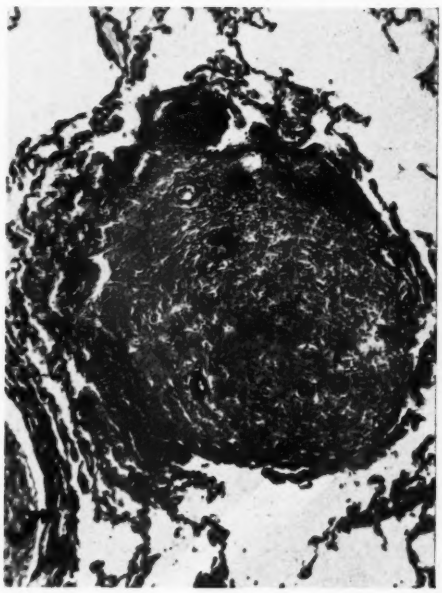
PLATE 20

FIG. 1. Collection of phagocytes filled with fine silica particles replacing a perivascular lymph node in the lung of the rabbit in the control group. Necropsy performed 23 months after intravenous injections with a 1 per cent suspension of pure silica. × 130.

FIG. 2. A more fibrotic silicotic nodule from the same animal as in Figure 1. The adventitia of a large vein is involved in the fibrotic process. In the left upper corner there is a collection of phagocytes loosely arranged in the same manner as that of the nodule seen in Figure 1. × 130.

FIG. 3. A fibrous nodule of late type in the lung of a rabbit of group IV, injected intravenously with the ash from a human lung. The nodule is at the site of former perivascular lymphoid tissue. × 130.

FIG. 4. Nodular silicotic phagocytes in the perivascular lymphoid tissue of the lung of a guinea-pig of group V, injected intraperitoneally 23 months previously with the ash of human lung with massive silicosis. × 130.



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Experimental Silicosis

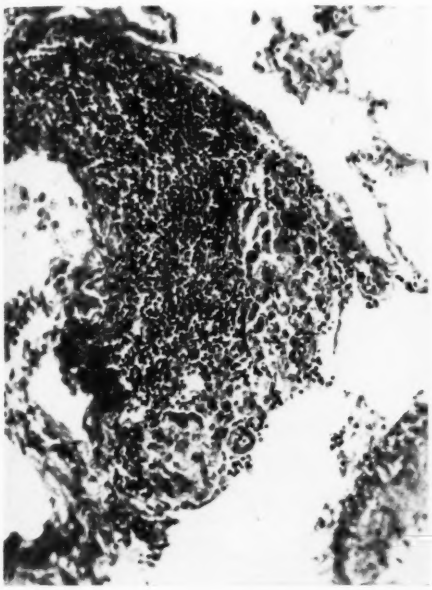
PLATE 21

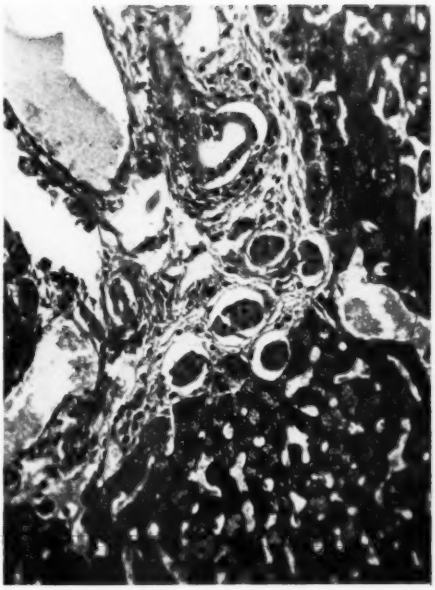
FIG. 5. Collection of silica and carbon phagocytes in the perivascular lymphoid tissue of the lung of a rabbit injected intravenously with ash of human lung (group IV). × 130.

FIG. 6. Collections of silica phagocytes in the periportal connective tissue of a rabbit injected intravenously with the ash from human lung (group II). Throughout the livers of the rabbits in this series there were similar collections of silica phagocytes in the liver sinusoids. × 130.

FIG. 7. Collection of silica phagocytes in the spleen of the same rabbit as shown in Figure 6. × 130.

FIG. 8. Perivascular collections of silica phagocytes in the spleen of a rabbit injected intravenously with a suspension of the ash from human lung (group V). Some of the nodular collections occupy germ centers and some are diffusely distributed throughout the pulp. × 130.





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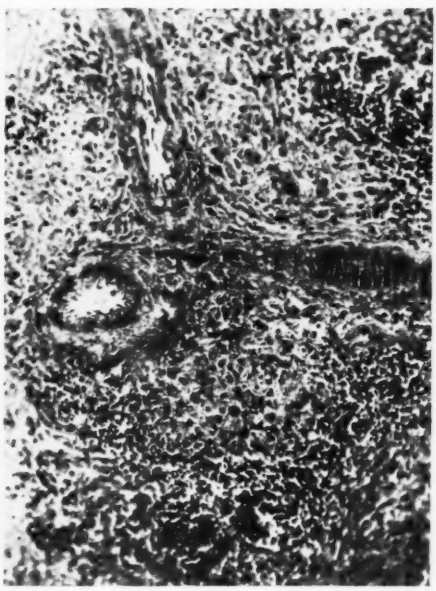

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PLATE 22

FIG. 9. Low-power view showing cirrhosis of the liver of a rabbit in the control group which had been injected 23 months previously with a 1 per cent suspension of pure silica. × 65.

FIG. 10. Higher power view of the same liver as in Figure 9 to show fibrotic nodule occupying a cirrhotic area. × 130.

FIG. 11. Cirrhosis of the liver of a rabbit injected 6 months previously with a 1 per cent suspension of ash from human lung (group V). × 65.

FIG. 12. Cirrhosis of the liver from a rabbit injected 23 months previously with a 1 per cent suspension of ash from human lung (group IV). × 65.

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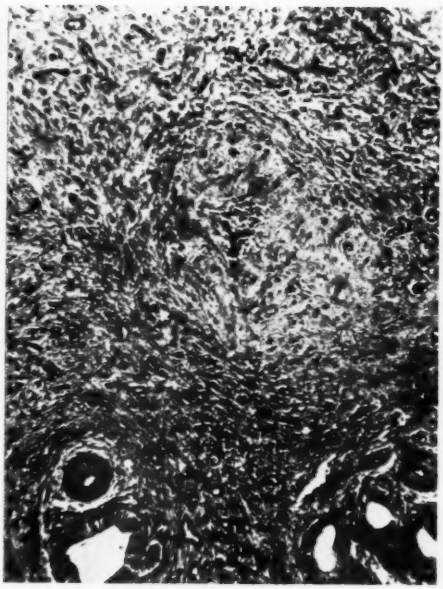

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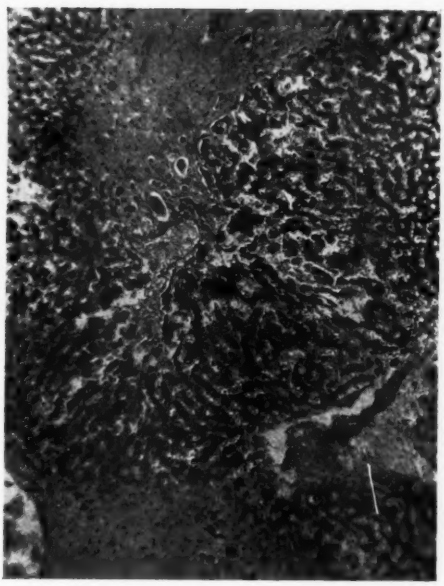

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Experimental Silicosis

PLATE 23

FIG. 13. Collections of silicotic phagocytes in the liver of one of the guinea-pigs injected intraperitoneally 23 months previously with a suspension of the ash from human lung (group V). × 65.

FIG. 14. Silicotic nodule in the liver of one of the guinea-pigs injected intraperitoneally with a 1 per cent suspension of pure silica. × 130.

FIG. 15. Small silicotic nodule showing collagenous change in a lymph node of one of the guinea-pigs injected intraperitoneally with a suspension of pure silica. × 65.

FIG. 16. Small silicotic nodule showing collagenous change in a lymph node of a guinea-pig injected intraperitoneally with a suspension of ash from human lung (group V). × 130.

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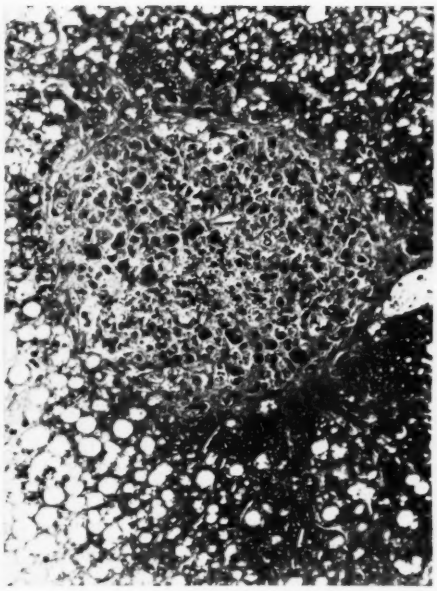

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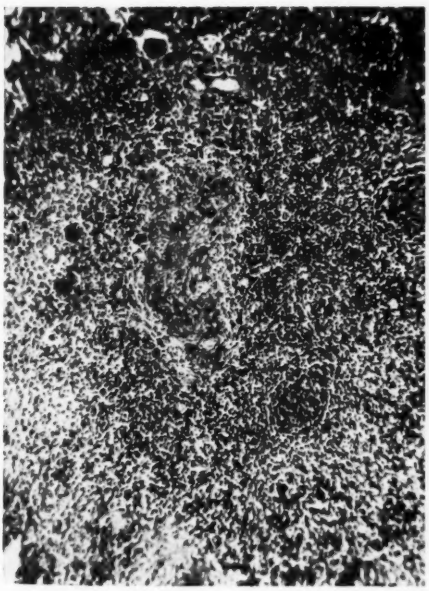

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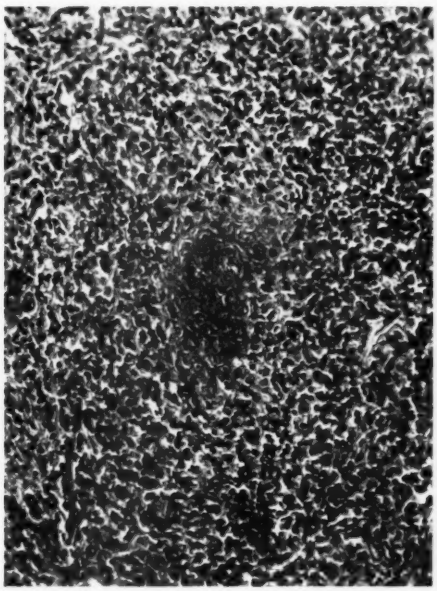

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Haythorn and Taylor

Experimental Silicosis

INFLUENCE OF AGE ON THE GROWTH OF LYMPHOMAS *

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(From the Department of Pathology, University of Oklahoma, Oklahoma City, Okla.)

More rapid growth of tumors is thought to occur in young than in old persons. Even though this idea is accepted clinically, an experimental clarification is warranted.

A feasible method of attacking this problem would be to compare the growth of transplantable tumors in animals of different age groups. Of such tumors, transplantable lymphomas of laboratory mice and rats were found to be satisfactory. When inbred strains of animals are used, transplants of lymphomas take in 90 to 95 per cent of trials and grow rapidly, a fact which makes data easy to obtain. The tumors are readily minced; and without dilution, by using a 1 ml. syringe, a known dose of cells can be administered to each animal. Because of the rarity of necrosis, the amount of living tumor may be fairly accurately measured and weighed.

The concept of "more rapid growth" of a tumor in the young has probably been most closely connected with the highly fatal tumors of childhood. It has also been considered that less malignant tumors increase more rapidly in size in young persons. For these reasons it was decided to study the following characteristics of lymphomas in animals of different age groups: (1) tumor growth by daily measurements and, in some cases, final weight of the tumor at the time of death; (2) changes in weight of tumor-bearing animal; (3) weight of tumor grown, as compared with the weight of the animal; and (4) mortality as measured by percentage of survivals. Microscopic studies were also made and mitotic indices computed. All comparisons of weights of animals were adequately controlled with litter-mates.

The young adult, and the old animals were fed on a standard Purina dog chow diet. The very young animals were unweaned at the beginning of each experiment; and although they were weaned during the experiment, this did not visibly affect the tumor growth.

Materials

Four lymphomas were used in this study. Three, when inoculated subcutaneously, remained localized until the disease was in its end-stage before they became generalized. These were a malignant thymoma (lymphoblastic type), lymphoma A of strain A mice, and a lymphosarcoma-leukemia of rats (Murphy). These three were used

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for study of the growth of the local tumor. The fourth, a generalized lympholeukemia, Y103, which results in a rapidly fatal generalized disease, without formation of large tumors, was used to study mortality rate. All of these tumors had been carried in transplant for a number of generations, and, at the time they were used, their growth had become constant within each strain.

Malignant Thymoma

On May 13, 1942, a female mouse, 7 months old (C57 Black × C3H), was found in great respiratory difficulty. The animal expired shortly and upon necropsy showed a large, conical mass occupying the site of the thymus and molded into the shape of, and filling, the whole upper thorax. It was attached to the posterior aspect of the sternum and had invaded the upper mediastinal structures. The tumor measured 15 by 10 by 6 mm. The cause of death was mediastinal compression. There was no general glandular enlargement, and careful gross examination did not reveal any other abnormalities. The diagnosis, on frozen section, was malignant thymoma of the lymphomatous type (lymphoma invading surrounding mediastinal structures). An immediate subcutaneous transplant to the groin was made into five C57 Black × C3H animals.* Sections from the tumor showed it to be made up of large, regular, round or oval cells with large nuclei and scarce cytoplasm, the cells resembling lymphoblasts. One to seven mitoses were found per oil-immersion field. The cells were arranged in no particular fashion and had destroyed normal thymic structures. No areas of necrosis were seen, and no tissues beyond those directly affected showed significant changes except for the bone marrow, which was extremely hyperplastic and possibly had early involvement. In transplantation the tumor grew at the site of inoculation to enormous proportions, 30 by 28 by 15 mm., or larger (Fig. 1), and late in the disease general blood stream involvement took place. One such animal showed a total white cell count of 87,000 per cmm. with 90 per cent lymphocytes and lymphoblasts. Almost every organ in the body showed neoplastic cells, which were found as a moderately heavy, dispersed infiltration in the liver and were most abundant in the lymphoid tissue and bone marrow. The microscopic pattern of the tumor is shown in Figure 2.

At the time of the transplantation for the growth studies, the tumor already had been passed through 4 generations of transplants. At this

* On May 28, 1942, an almost identical tumor occurred in a male mouse, 10 months old, of the same derivation, which had received a stilbestrol pellet subcutaneously some months previously. This later tumor had already escaped from its site of origin and had metastasized to the spleen and the liver.

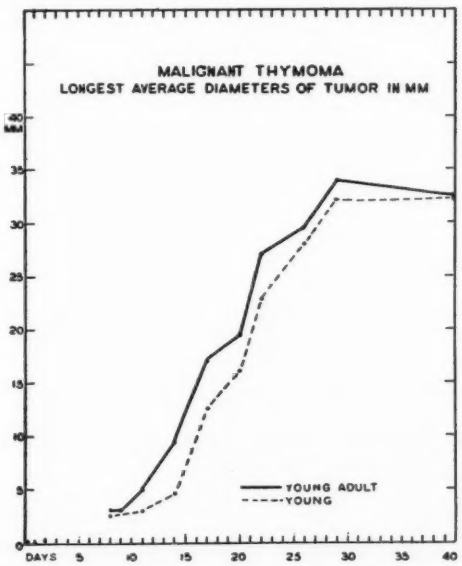
time it ordinarily killed between the sixth and eighth week after transplantation. The average size and weight of the tumors is given in Table I. On the morning of the experiment, an animal bearing a

TABLE I

Average Weight of Malignant Thymoma in Very Young and in Older Mice

Age (in days)	Number of mice	Average initial weight	Average weight (with tumor) at death	Weight range	Average weight of tumor at death
		(*gm.*)	(*gm.*)	(*gm.*)	(*gm.*)
12	21	4.8	22.4	1.4	8.0
42	34	17.1	31.0	6.0	12.3

thymoma which had grown for 4 weeks was killed, the tumor minced under aseptic conditions, and a dose of 0.05 ml. of minced tumor was injected subcutaneously into the right groin of each animal. The

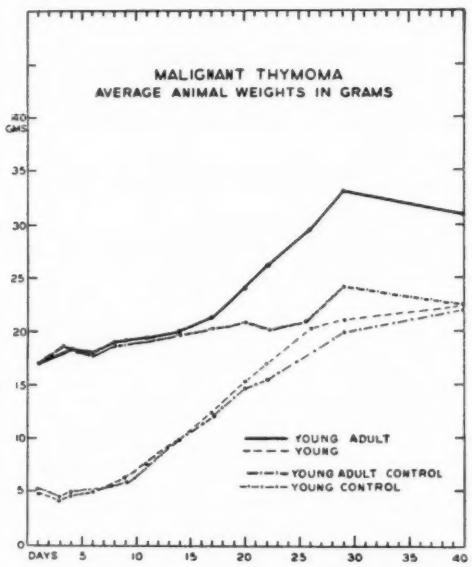


Text-Fig. 1. Longest average diameters of transplanted malignant thymomas measured by vernier caliper. The growths in the two age groups parallel each other.

tumors became palpable the next day, and their final masses in each age group were nearly identical. The average tumor sizes are shown in Text-Figure 1.

There was surprisingly little difference between the two age groups in tumor size, even though the initial weight of the very young animals was approximately only one-fourth that of the older ones. The gains in

body weight of the normal control animals as plotted were less than those of the tumor-bearing animals. The levelling off phase is difficult to understand except on the basis of general reduction in rate of body growth in both groups. Text-Figures 1 and 2 suggest two distinct phases in the growth of this tumor: an early rapid growth, and a late phase in which the growth drops off markedly. The groups were intact at the end of the experiments. Text-Figure 2 shows that the deceleration of the young animals in this late phase was not so extensive as that of the older ones. At first this phase of retardation was considered

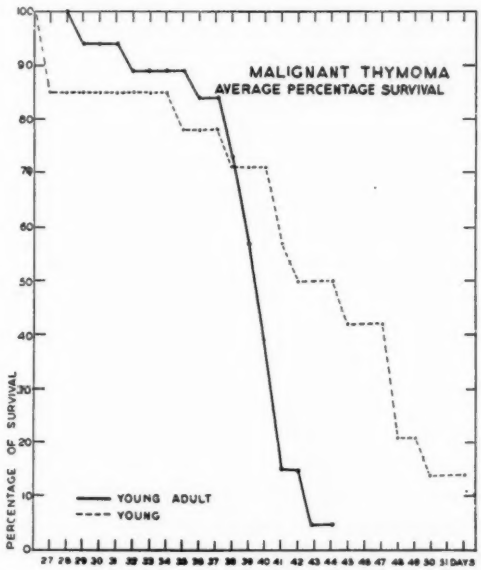


Text-Fig. 2. Average daily, or alternate day, weights of tumor-bearing animals after tumor inoculation and of noninoculated controls.

to be the lethal phase of the tumor until it was discovered that the weights of the control animals were showing a parallel retardation. From this, it appeared that the rate of tumor growth was somewhat dependent upon general body growth. When killed, the control animals in the young groups weighed approximately the same as their tumor-bearing litter-mates, and yet almost half of the total weight was tumor. In the group of mice 42 days old when implanted, the average tumor-bearing animal at death weighed 7.5 gm. more than the litter-mate control.

From the data it seems plausible to conclude that during the phase of rapid growth the tumor-bearing animal grows the same amount of

tissue, even though the tissue is neoplastic, as the litter-mate grows of normal tissue—and that the growth of neoplastic tissue must be at the expense of other tissues. In somewhat older animals, as long as there was no general effect upon the body, the tumor-bearing animal actually grew more tissue than did the litter-mate control, *i.e.*, the neoplastic tissue grew under the same general nutritional conditions as normal body tissues although more rapidly. In both age groups the average weight of the animal minus the tumor was less than that of the normal control. Although almost all of the animals were near



Text-Fig. 3. Survival in the different age groups.

the fatal limit of the tumor at the termination of the experiment, little general effect upon the body was noted. In this experiment the number of malignant cells injected into each animal of each age group was approximately the same, and the final mass of neoplastic tissue grown was greater in the older animals (Table I). Percentage survival curves showed that the younger age group lived longer (Text-Figure 3).

Lymphoma A

The next tumor to be studied was another lymphoma that arose spontaneously in a strain A mouse. It was discovered on May 9, 1940, in a male mouse, 4½ months of age. At that time the animal had generalized lymph node enlargement and a total leukocyte count of

92,000. The differential count showed 76 per cent lymphocytes and 23 per cent oxidase-negative blast forms. The post-mortem examination showed large mesenteric nodes (20 by 8 by 8 mm.), and cervical, axillary and inguinal nodes which averaged 10 by 8 mm. All of them were soft and gray-white with no gross necrosis. The thymus escaped. The spleen was purple-gray and tense, and measured 25 by 15 by 5 mm. Both liver and kidneys were gray and slightly enlarged. Histologic examination showed that the lymph nodes were filled with diffusely growing, round, basophilic cells with large nuclei, which had replaced the normal tissue. The same cells formed typical leukemic deposits in the liver, spleen, kidneys and bone marrow. There were many mitotic figures.

The diagnosis of leukemic lymphomatosis was made and the tumor

TABLE II

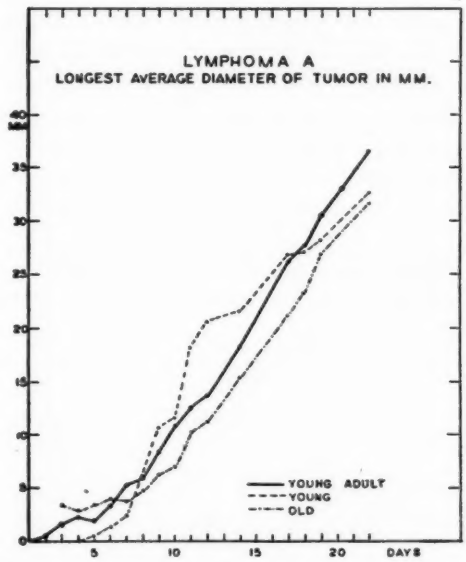
Average Weight of Lymphoma A, and Average Weight of Mice in the Three Age Groups

Age group	Number of animals	Average initial weight	Average weight at death	Average weight of tumor at death
		(*gm.*)	(*gm.*)	(*gm.*)
Unweaned (12 days)	18	6.9	21.3	13.9
4–5 months	17	28.3	37.6	13.8
13 months	20	27.8	32.5	9.8

then transplanted. At the time of the present experiment it had been transplanted nineteen times. The original sections were similar to those in the present transplants (Figs. 3 and 4). Sixty animals were used in the present experiment, 20 to each group. Except for dosage, the technic was similar to that used for the thymoma. The tumors of origin were minced together, and 0.05 gm. per 10 gm. of body weight was injected rapidly into the subcutaneous area of the groin. The dose was given in the proportion of a milligram of neoplastic tissue per gram of body weight to determine whether the amount of tumor injected would grow to tumors of varied size. Not more than 30 minutes was allowed to elapse between the time the animal bearing the original tumor was killed and the last animal received its tumor injection. Three age groups were used in this study. Although the dose of tumor inoculum was proportional to the weight of the animal, this made little difference since even the smallest dose of tumor cells produced neoplasms. Table II gives the data on the comparative weights in this series, and Text-Figure 4 a comparison of the longest average diameters of the tumors.

Grossly, there was surprisingly little difference in the way this tumor

grew in animals of each age group. Regardless of the size of the animal's body, the tumors in the oldest group weighed less than those in the other two groups. The animals were all killed on the 22nd day of the experiment. The mitotic index of the tumor was 4.7 in the young animals, 5.8 in the middle-aged and 4.8 in the old animals.* In this tumor the transplants appeared almost simultaneously in each



Text-Fig. 4. Longest average tumor diameter in millimeters for the three age groups bearing lymphoma A. No significant difference could be determined between the different groups at the time the animals were killed.

age group; a few of the oldest animals showed tumor before either the young or the middle-aged.

Lymphosarcoma-Leukemia (Murphy)

The third tumor studied was the rat lymphosarcoma-leukemia isolated by Murphy [1] in 1939. Although this tumor arose in an animal which received dibenzanthracene, it may possibly be spontaneous in origin. Its characteristics are similar to those of the other lymphomas. When the tumor was received, it had already been through a number of passages. I had carried it through more than 10 passages before

* The mitotic indices were determined by averaging the number of mitoses seen by multiple focusing in ten oil-immersion fields (× 900). In this experiment, the periphery of the tumor was chosen for mitotic counts; areas with necrosis, other tissues, or gross tissue spaces were not included.

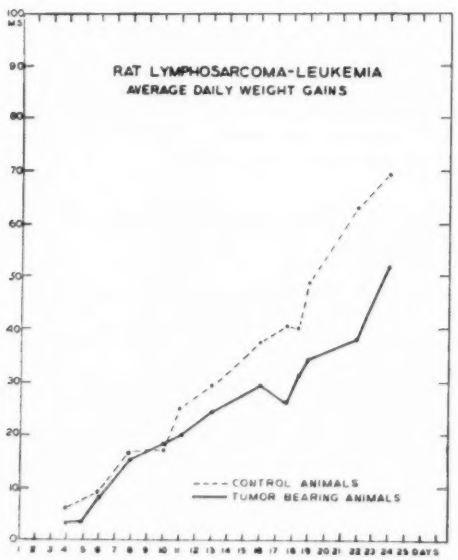
it was used in the present experiment. The percentage of takes in 102 animals inoculated with the tumor was 93. The tumors grew rapidly in the subcutaneous area of transplantation as large, soft, gray or gray-yellow masses with little or no necrosis (Fig. 5). Subcutaneous transplants killed the animals in an average of 12.6 days; a few animals survived as long as 25 days. Late in the disease there might be extension to the regional nodes. The drawing of a high-power field (Fig. 6) shows that the tumor is made up of large cells of lymphoblastic type.

The experiments with this tumor were made in a series of rats whose ages ranged from young, unweaned animals to young adults, and whose weights varied from 15.0 to 124.0 gm. Table III gives the data on the average weights, and Text-Figure 5 shows the contrast between tumor-bearing animals and controls. This suggests that the tumor may have

TABLE III

Average Weights of Unweaned and Young Adult Rats Bearing Lymphosarcoma-Leukemia (Murphy)

Age group	Number of rats	Average initial weight	Average weight with tumor at death
		(gm.)	(gm.)
Unweaned	18	20.5	35.5
Young adult	23	112.5	157.0

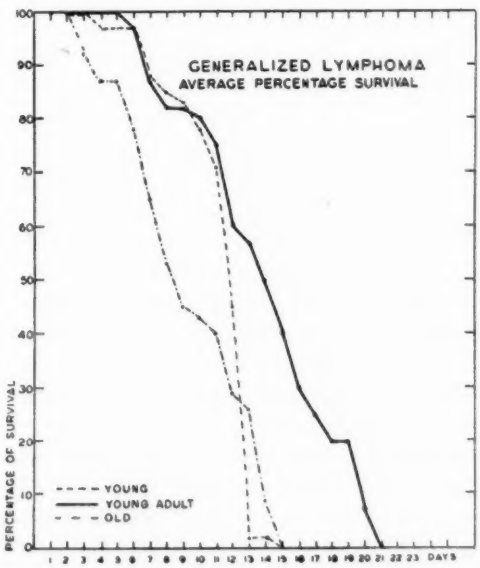


Text-Fig. 5. Weight gains of controls and of rats bearing rat lymphosarcoma (Murphy).

an early general effect, resulting in cachexia to the animals carrying it. Since few of the animals bearing the neoplasm survived beyond the second week, the curves for the last 10 days are not to be considered as absolutely accurate.

Lymphoma-Leukemia Y103

Lymphoma-leukemia Y103, a generalized leukemia of dba strain mice, was used in the study of the mortality rate in three different age groups. This tumor had been carried through many generations. Upon subcutaneous inoculation into the flank of an animal, generalized disease sets in very rapidly. There is general body dissemination, almost every organ becoming involved. The mesenteric lymph nodes become enlarged, the spleen is large and tense, and the axillary, inguinal and submaxillary nodes may also become involved. Microscopically, the neoplasm appears to be made up of large cells with large nuclei and scant cytoplasm. Histologically, this neoplasm resembles very closely the other tumors studied. The experiments on growth were carried on in two series of animals, 62 in the first, and 71 in the second. The animals of the first series were injected with 0.025 ml. per 10 gm. of body weight, and those in the second series received a total dosage of 0.05 ml. The results are summarized in Text-Figure 6 and Table IV.



Text-Fig. 6. Average percentage survival rates of animals bearing generalized lymphoma-leukemia Y103.

The mitotic indices were obtained as were those for lymphoma A, except that mesenteric nodes were used as the tissue from which to obtain counts. Typical fields were chosen. The involvement of the mesenteric node is constant in this disease, and no normal lymphocytes were included in the microscopic pictures. The mitotic indices were: young, 3.2; young adult, 3.4; and old, 3.5. As nearly as could be determined, age made no difference in the rate of tumor growth. A few older animals, however, died very quickly after the tumor was injected.

TABLE IV

Average Time of Death of Animals Inoculated with Tumor Which Produces a Generalized Lymphoma

Age group	Number of animals	Average time of death
		(*days*)
Unweaned	45	10.4
4–5 months	47	13.0
14 months	46	8.7

DISCUSSION

It is difficult to give an exact interpretation of the clinical rule that malignant neoplastic disease proceeds most rapidly in youth. Does this mean that a tumor in a child grows faster, is more difficult to eradicate, or kills more quickly than in an adult? The embryonal nature of many tumors in children (retinal glioma, adenosarcoma of the kidney, neuroblastoma of the adrenal, and teratoma) may endow them with a higher intrinsic growth rate than tumors in adults. The prognosis with malignant neoplasms in childhood is usually considered grave.[2] This, however, may be related to late diagnosis and the inapplicability of diagnostic and therapeutic procedures used in adults. The clinical manifestations are usually advanced when the patient is first seen.

The only fair comparison which could be made would be between tumors of the same kind in children and adults, and tumors known not to be under an endocrine influence. Clinically, when this comparison is made, it is rather surprising that the outcome, as measured by end results, is often about the same for each age group. The end results of treatment of teratoma in children are about the same as those in adults.[3] The only comparison that has been made on adenosarcoma of the kidney shows that prognosis is as favorable in children as in adults. Carcinoma of the breast in a large series showed no significant differential survival rate in age groups from 31 to 80 years.[4] Melanomas of infancy and childhood are of low-grade malignancy and seldom metas-

tasize,[5] in distinct contrast to the melanotic neoplasms of adults. There may be an endocrine influence in this malignancy. Reports are varied with regard to leukemia, which is usually of the acute type and rapidly fatal in children.[6] Hodgkin's disease in children is well known for its better prognosis. The prognosis of cancer of the reproductive organs in female children is extremely unfavorable.[7] It is difficult to escape the idea that carcinoma in the child tends to pursue a more rapid clinical course than in the adult. This may be true clinically because vital zones are of much smaller dimensions in the child and a tumor growing at the same rate in young and old would consequently kill sooner in the young. Since the tumors in the present experiments were subcutaneous, this factor was largely ruled out.

It is of importance to discover whether the rate of tumor growth actually parallels the rate of body growth. In young animals this would appear to be the case prior to general bodily effect of the disease. On the other hand, the same or greater amounts of neoplastic tissue were found in young adults and older animals which gained or lost but a few grams in weight during the experiment. This would suggest that tumor growth is not related to the anabolism of youth beyond the nutritional factors involved. As a matter of fact, it is amazing that the relatively large tumors were able to receive sufficient nourishment in small animals as easily as in larger animals. Although the experiments reported herein were short-termed, the rate of tumor growth could be contrasted in young animals that were rapidly gaining weight, young adult animals in which the growth rate was slower, and older animals in which it was relatively stationary. The one factor of growth of the animal may thus be compared with the growth of the tumor. The experiments are useful because a tumor of constant growth rate was used and was placed in varying age environments, yet it could not be shown that age influenced either the rate of tumor growth or mortality. It appears, therefore, that the property of growth in these transplantable tumors is probably completely dissociated from that of general body growth except for nutritional requirements. We may assume, up to the point of general bodily debility, that the nutritional requirements in these experiments were adequate.

The mortality curves and rates in the age groups were not essentially different. In a number of old animals whose deaths occurred within 3 to 4 days after tumor inoculation, microscopic examination of the tissues showed that death was caused by neoplastic infiltration. This fact suggests that the debilitated state of the old animals renders them more susceptible to the fatal outcome of tumor growth.

The experiments might be criticized because variable doses of tumor

inocula were used, if it were not for the constancy of results and the large groups of animals used. A dose relative to body weight—so many milligrams of tumor to so many grams of body weight—was tried, then a standard dose was used in all age groups regardless of weight. In both, sufficient cells were used to produce tumor takes, but no variation in rate of tumor growth with dose could be found.

In at least one tumor, the malignant thymoma, it was possible to show that the rate of tumor growth actually paralleled the rate at which normal control animals were laying down tissue. In a way, this would characterize neoplastic tissue. Even though a smaller animal was not able to deliver the same amount of nutrition to the tumor area, nonetheless, the tumor utilized the necessary nutritional elements to show unrestrained growth. This did not restrain growth, regardless of the animal's age. The unrestrained growth of tumors fits in well with the known embryonic-histologic and metabolic characters of tumor cells.

Since it was not possible to correlate tumor growth with normal whole body growth (age), it seemed plausible to try to relate tumor growth to the regrowth of tissues in healing wounds. Some experiments indicate that healing in the young is more rapid because it begins earlier and is not caused by an actual increase in rate of growth.[8] If the growth phases are then compared, the factors, except for nutrition, that control the rate of growth are different from those that control the rate of wound healing. Perhaps the laws which govern wound growth are very closely related to those of normal tissue growth, whereas those of neoplastic tissue are far removed. Mitotic indices lend support to Ewing's[9] statement that behavior of a neoplasm is determined mainly by the "properties" of the tissue of origin, *i.e.*, by its original histologic-growth characteristics.

Summary

Four transplantable lymphomas were studied in animals of different ages. With regard to local lymphomas, the gain in weight during tumor growth was accounted for in the young animals by gain in the normal tissues (one-half), and also in the tumor. In older animals the gain in weight could be accounted for only by the amount of neoplastic tissue grown (the animal's tissues lost weight). In one instance the average tumor weight of the older age group was greater, in another instance slightly less, than that of the younger age group.

It was demonstrated with the malignant thymoma that these neoplasms increased in mass one-half as rapidly in young animals as did normal young growing tissues. All of the local tumors differed

from normal tissues in their ability to continue this growth unchanged beyond the slowing down of normal tissues.

No significant difference in mortality could be demonstrated in animals of different age groups when inoculated with a generalized lymphoma.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 24

FIG. 1. Late generation transplant of the malignant thymoma. Areas of necrosis appear on the surface, and the opposite inguinal lymph node shows evidence of metastasis. About normal size.

FIG. 2. Drawing of a field from the transplant. In this particular field the cells are loosely arranged; in other areas they were tightly packed. The cells are rounded, 12 to 15μ across, have scant cytoplasm, and their nuclei have a heavy chromatin network. The stroma is scant. Hematoxylin and eosin stain. About $\times$ 900.

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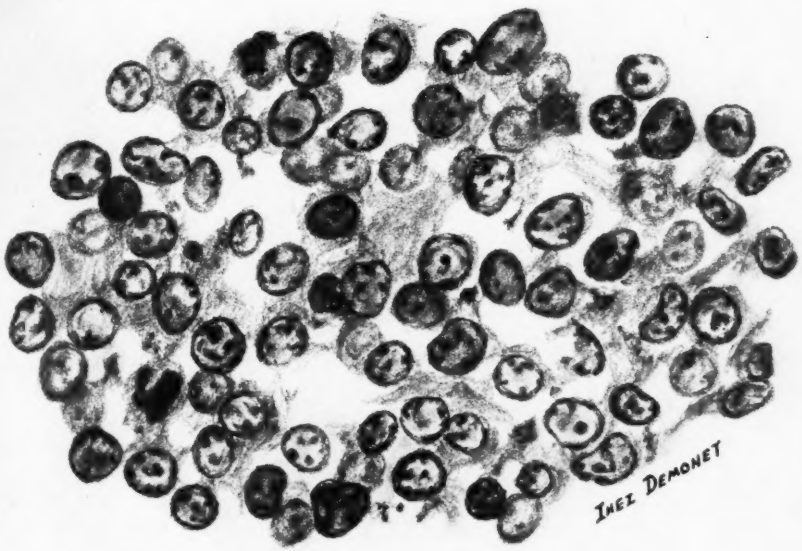

Nettleship Influence of Age on Growth of Lymphomas

PLATE 25

FIG. 3. Transplant showing the locally invasive character of lymphoma A. The malignant cells have grown into and surrounded muscle fibers. Hematoxylin and eosin stain. × 87.

FIG. 4. Detailed character of the malignant cells. Fibers of striated muscle are at the top and bottom of this field. Hematoxylin and eosin stain. × 1000.

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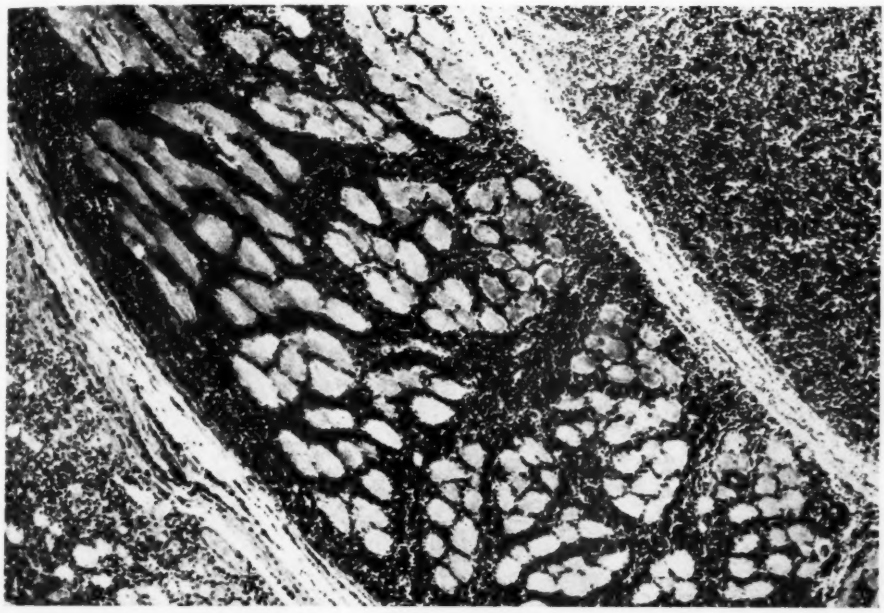

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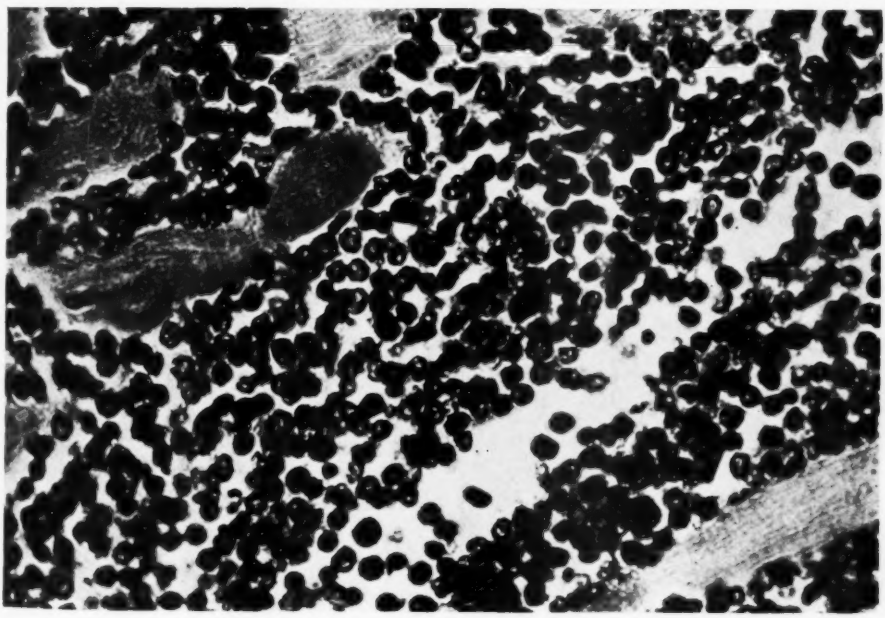
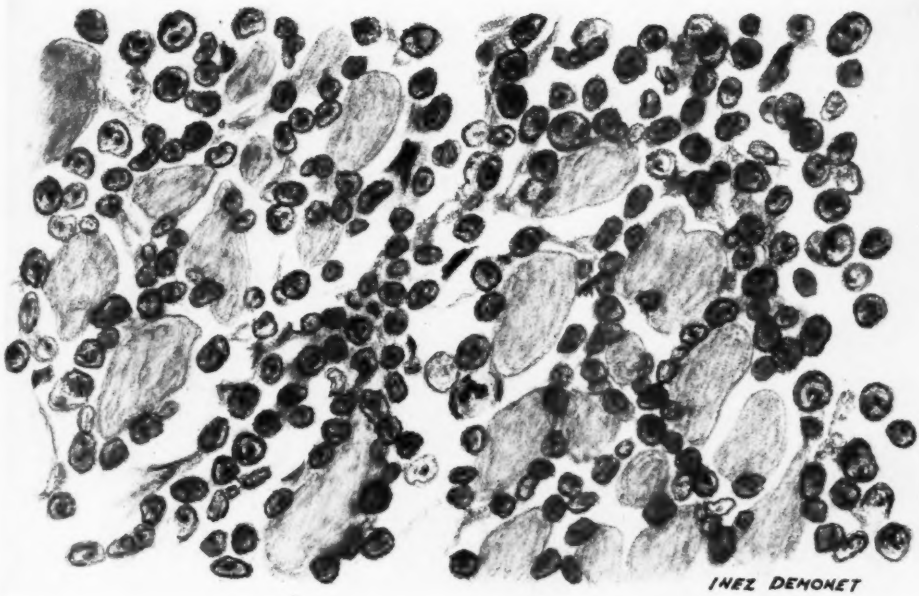


Nettleship Influence of Age on Growth of Lymphomas

PLATE 26

FIG. 5. Bilateral inguinal transplants. The tumors were at about their limit of growth; they were 2 weeks old and measured between 30 and 40 mm. in longest diameter.

FIG. 6. Drawing of high-power field to show character of cells and local invasion of abdominal muscle wall. Hematoxylin and eosin stain. × 1000.



Nettleship Influence of Age on Growth of Lymphomas

GROWTH OF A MOUSE LYMPHOMA COMPARED TO NORMAL TISSUE GROWTH *

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One aspect of the growth of a neoplasm is its ability to increase in mass more readily than normal tissues. It is uncertain how rapidly neoplasms accumulate protoplasm in comparison to normal tissues. Such data should help us determine the extent to which normal growth restraints have been lost. Although few accurate observations are available on the rate of protoplasmic accumulation, tumor growth has been considered to take place at about the same rate as that of embryonic tissues.[1]

Additional data on this aspect of tumor growth were obtained by utilizing inbred strains of mice which have transplantable lymphomas. Experimentally, it was but necessary to compare daily weights of growing animals with those of the same age which bore tumors.

MATERIALS AND METHODS

The lymphoma used in this experiment arose spontaneously in $C57 \times C3H$ mice. It grew locally when implanted subcutaneously, and only late in its course gave rise to extensive spread and leukemia. Its history and morphology have been described, as well as the technic of its transplantation.[2]

Animals of two age groups were inoculated with this lymphoma. The younger group averaged 12 days and had an average weight of 4.8 gm. The older group averaged 42 days and had an average weight of 17.1 gm., almost four times that of the smaller animals. How these groups of animals grew, with and without tumors, is shown in Table I. The weights at death are given in Table II.

DISCUSSION

Perhaps the most significant fact to emerge from Table I is that in young animals which are growing rapidly the total tissue which they are capable of growing is the same regardless of its normal or neoplastic nature. This in turn points up two facts. The tumor, while it is disorganized in growth, does not in reality grow any faster than the varied tissues of young control animals, but the organs of the animal which is bearing the tumor probably suffer from lack of nourishment (Table II). When the older age groups are examined, we see that the

* Received for publication, April 3, 1944.
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animals which bore tumors actually outstripped the controls in weights (31 to 22.4 gm.). In this group, however, the organs of the animals which bore tumors did not suffer to the extent that they did in the younger animals.

TABLE I

Average Weights of Mice in Two Age Groups with and without Tumors

	Average weights, young mice		Average weights, young adults	
Day of experiment	Animals with tumors	Control animals	Animals with tumors	Control animals
	(gm.)	(gm.)	(gm.)	(gm.)
1	4.8	5.1	17.0	17.2
3	4.3	4.5	18.1	18.3
4	4.5	4.7	18.3	18.3
6	4.8	5.0	18.1	18.0
8	5.7	5.7	19.0	18.6
9	6.2	6.0	19.1	19.1
11	7.6	7.5	19.4	19.3
14	9.6	9.7	20.0	19.7
17	12.4	12.2	21.3	20.1
20	15.4	14.7	24.0	20.8
22	17.0	15.5	26.2	20.3
26	20.2	17.7	29.4	21.1
29	21.0	19.7	33.2	24.3
40	22.4	22.2	31.0	22.5

Schrek,[1] in 1936, in comparing the Walker rat tumor with embryonic rat growth, concluded that both growth rates could be represented by linear curves, and that their actual rates were of the same order of magnitude. He was impressed, as was I, by the fact that the malignant cell does not appear to be endowed with an excessive capacity for growth.

TABLE II

Weights in Two Different Age Groups Which Bore Lymphomas, as Compared to Litter-mate Controls

Age group	Average initial weights		Average final weights		Average weight gains		Amount of normal tissue gain		Amount of tumor gain
(days)	tumor (gm.)	control (gm.)	tumor (gm.)	control (gm.)	tumor (gm.)	control (gm.)	tumor (gm.)	control (gm.)	
12	4.8	5.1	22.4	22.2	17.6	17.1	9.6	17.1	8.0
42	17.1	17.2	31.0	22.5	14.0	5.3	1.7	5.3	12.3

SUMMARY

Young mice which grew transplantable lymphomas accumulated approximately the same amount of tissue as their litter-mate controls, and the rate of accumulation was similar. One-half of the total gain in weight in the tumor-bearing animals was in the tumor. Older animals which bore tumors grew more tissue than their litter-mate controls.

Their tumor weights could account for almost all of their weight increase.

Even in young animals, the total neoplastic mass accumulated was never greater in any time period than that grown by heterogeneous tissues in litter-mate controls. The actual growth of the protoplasm in this lymphoma appears to be approximately one-half that of heterogeneous normal tissues.

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PROLIFERATIVE LESIONS IN MULTIPLE MYELOMA WITH SPECIAL REFERENCE TO THOSE OF THE SPLEEN

The Origin of the Plasma Cell*

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Plasma cell myeloma has been considered a local bone tumor (Geschickter and Copeland), a local tumor of reticulo-endothelial origin with or without multiple metastases (Hellwig), or a diffuse proliferation of the reticulo-endothelial system (Ewing). Ulrich has proposed a classification of plasma cell tumors into somewhat similar groups. Further, the type cell has been generally accepted, since the series reported by Christian, as the plasma cell. A widely held view is that these cells arise from lymphocytes (Maximow), but this as well as the relationships of this cell has been the subject of much conjecture (Michels). For these reasons, an examination of portions of the reticulo-endothelial system in cases of multiple myeloma might give information both as to the nature of the disease process and as to the origin and relations of the plasma cell.

Material

The material consists of 12 autopsied cases of multiple myeloma, the total number in the pathology laboratories of the University of California and Mt. Zion Hospitals. Most of the tissues had been fixed in formalin, a few in Zenker's fluid. The material had been stained with hematoxylin and eosin, Giemsa's stain, and in a few cases with malachite green-acridine red or with Wright's blood stain. A summary of the pertinent clinical and post-mortem findings is given in Table I.

Findings

The clinical and hematologic aspects will not be further amplified. These have been covered by numerous authors (Ulrich, Wintrobe and Buell, Osgood and Hunter, Churg and Gordon). However, anatomic findings in selected organs will be described in detail.

The spleen was enlarged in all but one of the cases in which the organ was weighed, and the weight of this spleen was near or beyond the upper limit of normal for the patient's age (case C. D., 150 gm.). Microscopically, malpighian follicles were preserved in all of the cases and even in the spleen most enlarged (case F. B.) the follicles were still found as small lymphoid islands separated by wide areas of plasma

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cells. The lymph follicles were of quite usual appearance as is shown in the illustrations from these cases. Likewise, all of the spleens showed plasma cells. The site of plasma cell proliferation could be determined only in those spleens which were well preserved, *i.e.*, in 7 cases; in the 5 showing marked post-mortem alteration no conclusions could be reached as to the relationships of these cells to other finer structures. Post-mortem alteration appears to be the limiting factor in the cases in which this specific lesion could not be made out. The lesion is shown in the accompanying plates and consists of a local proliferation of plasma cells which are either replacing a sinus endothelial cell, or in other cases are superimposed into the sinus lumen upon an intact lining cell. The appearance suggests that endothelial cells divide in two planes, in one plane each producing a littoral cell and beside it a plasma cell. The latter replaces the flat endothelial cell which would normally be in this location. In the other plane the continuity of the sinus lining is maintained by the littoral cells and the plasma cells are superimposed into the vascular lumen on the cells of origin. Most of these plasma cells are still attached and occasionally form clusters hanging into the blood stream. Elsewhere they are free within a small channel, apparently broken from their site of attachment. The lesion will be discussed later.

The lymph node involvement was somewhat similar in that all of the lymph nodes examined contained at least some plasma cells. Some nodes, however, were massively replaced, showing loss of architecture and invasion of the capsule by sheets of plasma cells. Others, even in the same cases, were less completely replaced and these are considered in particular, for, in all, the masses of plasma cells formed bands between the lymph follicles. The lymph follicles with their germinal centers remained as the last normal landmarks and were separated by wide zones of tumor cells. Thus, plasma cells were present in the interfollicular portions of the nodes and the areas of lymphoid proliferation were unaffected till later, or showed but a few stray cells of the plasma cell variety. No relation of plasma cells to sinus lining could be established, the plasma cells usually forming sheets obliterating littoral cells and all sinus structures.

The liver was definitely enlarged in 6 cases. Three of these livers showed infiltration of leukemic type with plasma cells. The liver in another case (B.K.), though not greatly enlarged, showed early infiltration of the same variety. There were plasma cells in large collections in the portal areas and in groups throughout the remainder of the lobule. The remaining livers were notable only for their lack of involvement and, in all, the Kupffer cells were clearly distinguished and of usual appear-

TABLE I

Summary of Findings in 12 Cases of Multiple Myeloma

Case	Age	Sex	Duration according to history	Serum protein (*gm./100 cc.*)			Bence-Jones proteinuria	Red blood cells	Hemoglobin	White blood cells	X-ray*	Liver		Bone marrow infiltration	Lymph node infiltration	Spleen	
				Total	Albumin	Globulin						Weight	Leukemic infiltration			Weight	Lesion noted
			(*mos.*)					(*000,000*)	(*gm.*)	(*000*)		(*gm.*)				(*gm.*)	
N. S.	64	F	10	17.6	1.6	16.0	o	1.92	6.6	13.0	o	2100	o	+	+	590	o
L. P.	54	M	11	8.6	4.9	3.7	+	3.09	9.9	6.2	+	2065	o	+	+	390	o
F. B.	59	M	3	6.6	4.2	2.4	+	2.85	9.5	10.0†	+	2720	+	+	+	760	+
E. G.	53	M	4				+	3.07	8.7	6.5	o	"Normal"	o	+	+	450	+
I. W.	55	M	5				o	2.00	5.4	10.3	o	"Large"	o	+	+	"Normal"	o
M. B.	70	F	12	6.0	3.4	2.6	o	3.71	9.8	14.9	o	"Normal"	o	+	+	"Normal"	+
B. K.	55	M	14	13.3	2.9	10.4		1.35	4.8	10.0	o	1820	+	+	+	280	+
R. B.	53	M	7	14.2	2.5	11.7	+	3.80	6.0	11.2	o	"Normal"	o	+	+	"Normal"	o
C. D.	50	M	48	7.8	5.6	2.2	+	2.40	7.8	8.3	+	1525	o	+	+	150	o
R. J.	52	F	120‡			§		1.23	4.8	3.4	+	2435	+	+	+	230	+
H. H.	65	M	18	6.2	3.1	3.1	+	1.80	5.2	6.3	+	"Large"	+	+	+	"Large"	+
H. M.	44	M	22	7.4	4.7	2.7	+	1.75	6.0	6.6	+	1720	o	+	+	300	+

* Or radioactive phosphorus.

† Five per cent plasma cells in differential leukocyte count.

‡ Thigh amputated for local tumor 4 years before death.

§ Terminal hyperglobulinemia suggested by marked auto-agglutination of blood.

ance. This infiltration is of interest in that it is not the type usually characteristic of lymphatic leukemia, but rather resembles the distribution often seen in the monocytic or the myelogenous types.

Bone marrow from multiple regions was examined and all specimens showed numerous plasma cells. In general, these cells replaced all marrow elements, including the vascular channels. Usually the bone trabeculae were small. This massive involvement illustrates the diffuseness of the process, but obliterates any relationship of the plasma cell to a specific cell as precursor.

Discussion

A. The Origin of the Plasma Cell

In this disease two organs give clues as to the origin of the plasma cell. First, the spleen suggests by its appearance that it is a site of local proliferation of plasma cells. Maximow described the splenic sinuses as cylindrical meshes lined by squamous reticular cells, a part of the general reticular or histiocytic framework. Knisely believed that this system is closed. In plasma cell myeloma the cells that are proliferating into the sinus spaces appear to be derivatives of these lining cells. Their mode of proliferation is like that described by Doan, Cunningham and Sabin for megaloblasts and for clasmatocytes, that is, they hang as single cells or as clusters into the vascular stream. The cells actually form a part of the vessel wall and do not appear to have been lodged there by chance from the blood stream, or to have reached this site by invasion from an extravascular source. However, since the littoral cells are apparently closely related to the cells of the diffuse framework of the pulp, it is quite possible that plasma cells are arising also in the perisinusoidal tissue. This origin from the framework reticular cells might account for the plasma cells distributed throughout the spleen. Likewise, the preservation of intact lymph follicles, even with extensive plasma cell involvement of the spleen, speaks against the lymphocytic origin of these cells.

Second, the lymph nodes suggest likewise a histiocytic origin of the plasma cell. Downey described the lymph sinuses as lined by squamous histiocytic cells only near the afferent and efferent radicals. The finer sinuses are directly continuous with the general reticulum of the pulp. The lymph nodes in this group of cases showed diffuse proliferation in sinus areas with lymphatic tissue remaining intact. The diffuse nature of this growth in lymph nodes, where plasma cells are not seen arising from sinus endothelial cells as they are in the spleen, might well be due to the absence in lymph nodes of a completely closed system of littoral cells. Recently, Parsons has shown the new growth of plasma cells

from littoral cells in lymph nodes of mice treated with x-ray and with carcinogens and has suggested the histiocytic origin of plasma cells. This is in accord with the lymph node involvement in these cases. It seems unlikely that the plasma cells in lymph nodes are of metastatic origin from a local tumor, because of the involvement of lymph nodes in many areas and their progressive replacement, even in the absence of metastatic nodules in such common sites of spread as lung and liver.

The liver is of interest for several reasons. First, the absence of changes in the Kupffer cells fits well with the contention of Sabin that these cells are completely differentiated derivatives of the reticulo-endothelial system. It is also of interest that when infiltration of the liver does occur (cases F. B., B. K., R. J., and H. H.), the cell distribution is similar to that commonly seen in myelogenous and monocytic leukemia, rather than to that of lymphatic type. The distribution in the cases reported by Osgood and Hunter and by Churg and Gordon was also of this type. In this connection, another suggestive resemblance of this tumor to tumors of histiocytic, rather than lymphoid, relations is brought out in the series of malignant lymphomas studied by Gall and Mallory. In that series clasmatocytic lymphomas were the only tumors of the group which involved bone with any degree of regularity.

In review of these anatomical relations, the lymphoid origin of the plasma cell is contradicted by the persistence of lymphoid follicles in the spleen and lymph nodes even when these lymphoid masses are separated by wide areas of plasma cells. Likewise, the type of hepatic infiltration, when it occurs, speaks against a lymphocytic relationship. On the other hand, an origin from histiocytic type cells is indicated by the sites of proliferation in spleen and in lymph nodes, by the type of hepatic infiltration, and is suggested by the invasion of bone.

B. The Nature of the Process

There are numerous reports of local plasma cell tumors, and extramedullary examples have been gathered recently by Hellwig. Yet all of the cases in the series reported here showed extensive involvement of the reticulo-endothelial system, the histiocytic or reticular portions in particular. This was irrespective of their original onset, for one that showed widespread involvement (case R. J.) was treated for a local bone tumor by amputation of the thigh 4 years before death. It is true that these cases are, in a way, a selected series in that all were fatal. However, it would seem that this disease must be considered at least potentially diffuse, no matter how localized the original lesion may seem.

C. Relation of the Plasma Cell to Hyperglobulinemia

It would appear, then, that the plasma cell in origin is related to the monocyte, the clasmatocyte, or macrophage of Cunningham, Sabin and Doan, or to the tissue histiocyte of Maximow. These are the cells which Sabin has shown to be concerned directly in the formation of antibodies. The occurrence of the plasma cell in physiologic states of increased antibody-globulin formation and in conditions of abnormal excess globulin production suggests that this is a valid functional relationship as well. Bing and Plum, and, more recently, Kagan have discussed hyperglobulinemia and have shown that the most common causes of this condition are chronic infections, particularly tuberculosis, syphilis, leprosy, lymphogranuloma venereum, subacute bacterial endocarditis and kala-azar. These, according to Bing, are associated with changes in the reticulo-endothelial system, notably with the accumulation of plasma cells. An interesting report in this connection is that by Bjorneboe and Gormsen, who produced tissue infiltration of plasma cells, especially in the spleen but also in the liver and in other organs, by repeated immunization of rabbits with killed pneumococci. These animals showed definite elevation of serum globulin, which was proportional both to the degree of plasma cell infiltration and to the agglutination titer of the serum.

Among the noninfectious causes of hyperglobulinemia, multiple myeloma is listed first. Only 2 of the 9 cases of this series in which the serum globulin was determined showed normal serum globulin levels (considering 2.58 gm. per 100 cc. as the average normal as given by Peters and Van Slyke). In such cases Bing and Plum believe the type cell to be more mature and less rapidly proliferating. These authors stated that the highest values are found in those cases with extremely immature cells. Sabin has shown that globulin release by clasmatocytes is associated with the shedding of cell cytoplasm into the blood stream, a process for which maturity is perhaps unnecessary. However, this series of cases is too small to correlate the duration of the illness with serum globulin level and this point must remain for further investigation. Hyperglobulinemia occurs also in leukemias, notably monocytic, but there are rarer reports of increases in myeloid and lymphatic types as well (Bing and Plum, Kagan).

No discussion is attempted here of the renal lesion or of Bence-Jones proteinuria. These aspects are discussed in particular by Bell, and by Forbus, Perlzweig, Parfentjev and Burwell.

Summary

A lesion of the reticulo-endothelial system in multiple myeloma is described, in particular as it is found in the spleen and lymph nodes.

In the spleen this lesion consists of the intrasinusoidal proliferation of plasma cells from sinus lining. In addition, plasma cells are found throughout the red pulp. In lymph nodes plasma cells proliferate in the interfollicular tissue. Lymphoid structures remain intact in both these organs. The presence of a closed system of littoral cells in the spleen, in contrast to that of lymph nodes, is suggested as the explanation for the localization of plasma cells in relation to sinus lining only in the former organ. These lesions, as well as the distribution of leukemic infiltration when the liver is involved, and the tendency to involve bone, suggest that plasma cells do not arise from lymphocytes or their immediate precursors, but that they arise, at least in this disease, from tissue histiocytes. It thus appears that plasma cell myeloma is more closely related to diseases of monocytic or clasmatocytic type than of lymphoid type. It is pointed out that the disease, multiple myeloma, at necropsy consists of a diffuse proliferative process involving the entire reticulo-endothelial system, regardless of its predominant skeletal or local onset. In origin the plasma cell is related to those cells which have been specifically shown to be concerned in antibody formation. Previous observations on the occurrence of the plasma cell suggest that it, too, forms globulin and is concerned with the formation of antibody globulins and in abnormal states with hyperglobulinemia.

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DESCRIPTION OF PLATES

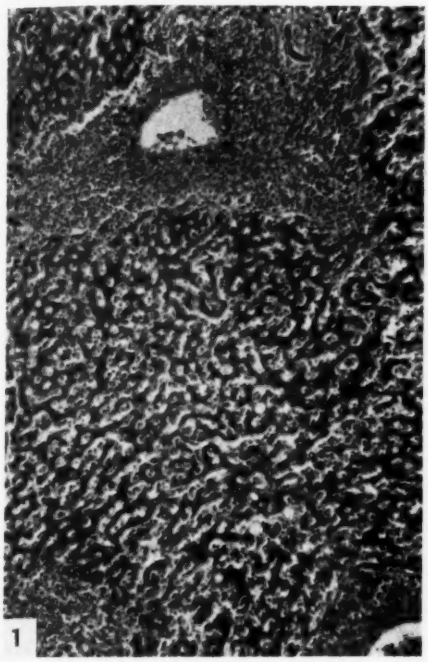
PLATE 27

FIG. 1. Infiltration of the liver (case F.B.) showing plasma cells throughout the lobule as well as in portal areas. The same type of infiltration was present in the other three livers involved (cases B.K., R.J., H.H.). × 75.

FIG. 2. Spleen (case R.J.) showing lymphoid tissue surrounded by plasma cells. × 95.

FIG. 3. The same spleen as in Figure 2 to show several sinuses lined by plasma cells. The one in the upper center is lined in part by flat littoral cells and in part by plasma cells. × 580.

FIG. 4. The same lesion as in Figure 3 in greater detail. × 1160.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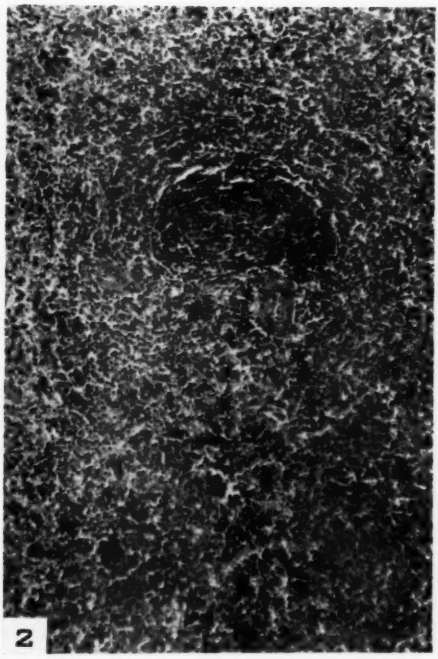
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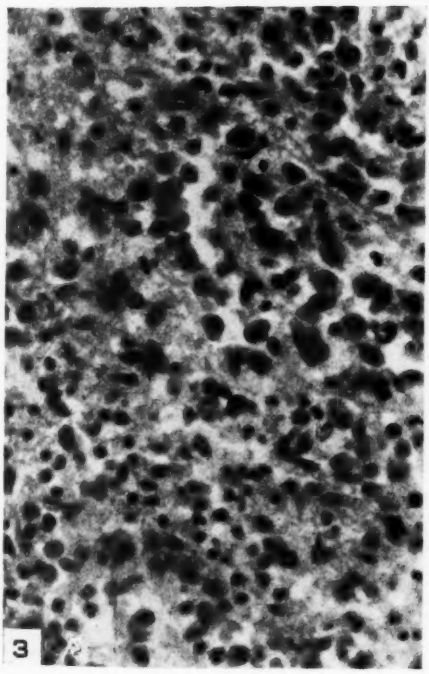
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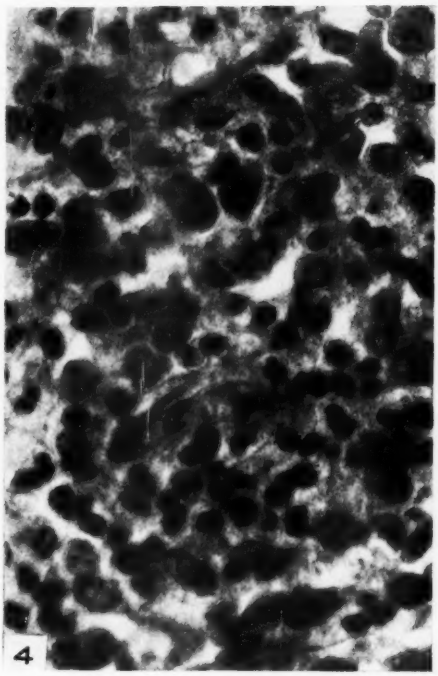
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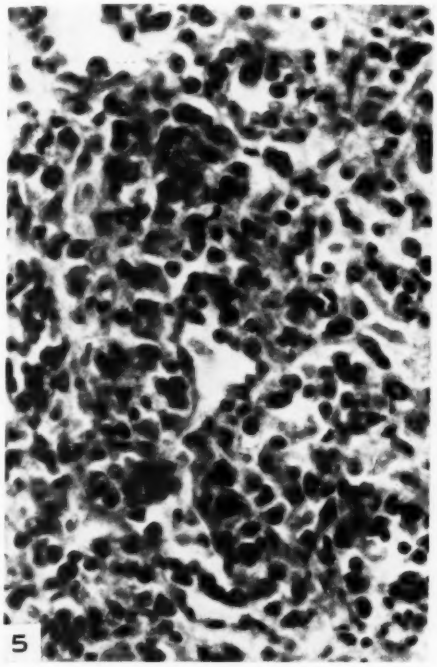
PLATE 28

FIG. 5. Spleen (case F.B.) showing several sinuses with a proliferated lining of the same type as shown in the preceding figures. There are numerous plasma cells in the perisinusoidal tissues. × 580.

FIGS. 6, 7 and 8. Details of sinuses of the same spleen (case F.B.). Plasma cells project into the blood stream. Some replace littoral cells and some are superimposed on them. × 1160.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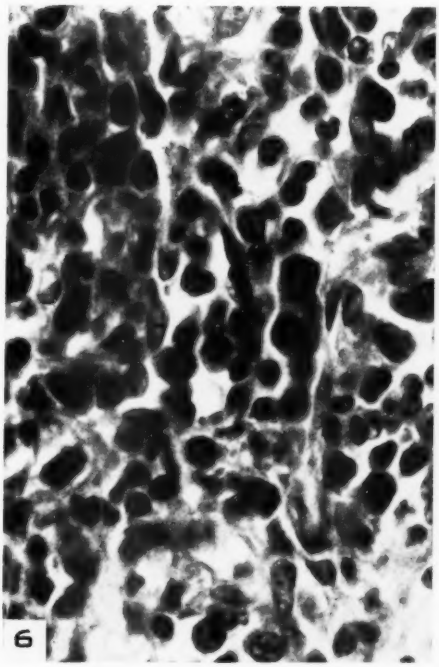
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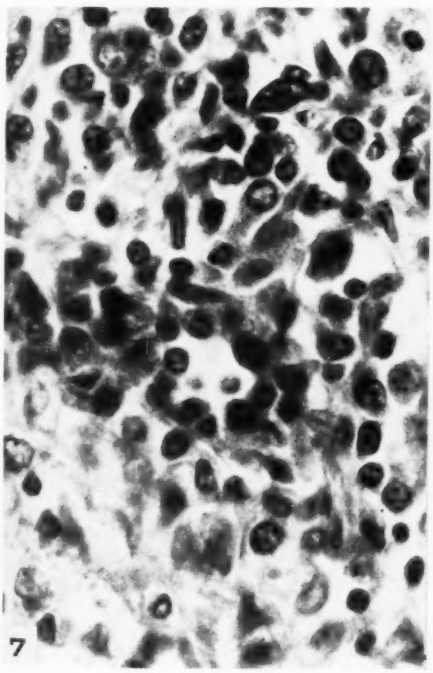
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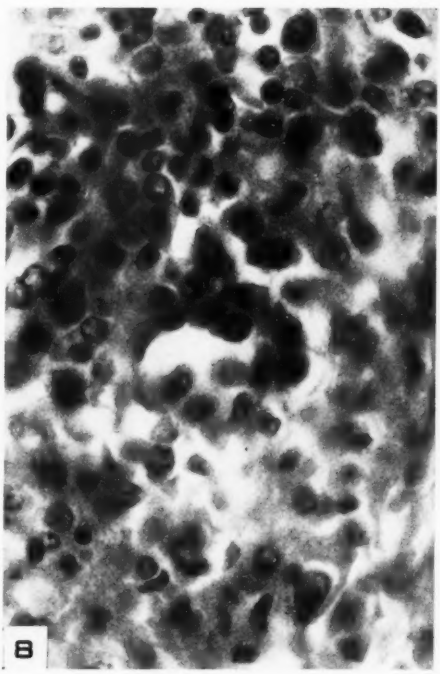
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PLATE 29

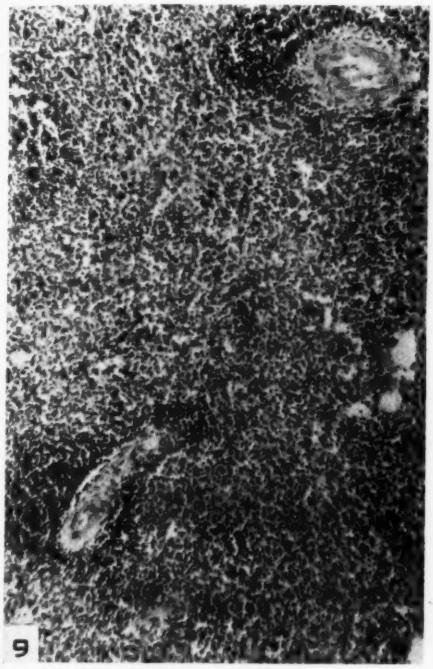
FIG. 9. Spleen (case H.H.) with malpighian follicles separated by masses of plasma cells. × 95.

FIG. 10. The same spleen as in Figure 9 with many sinuses lined by proliferated plasma cells. Some form clusters projecting into the lumen. × 580.

FIG. 11. A single sinus from the same spleen as Figures 9 and 10 to show this lesion. × 1160.

FIG. 12. Spleen (case B.K.) with persistent malpighian corpuscles. × 95.

FIG. 13. Details of the same spleen (case B.K.) with cells attached at their sites of proliferation. × 1160.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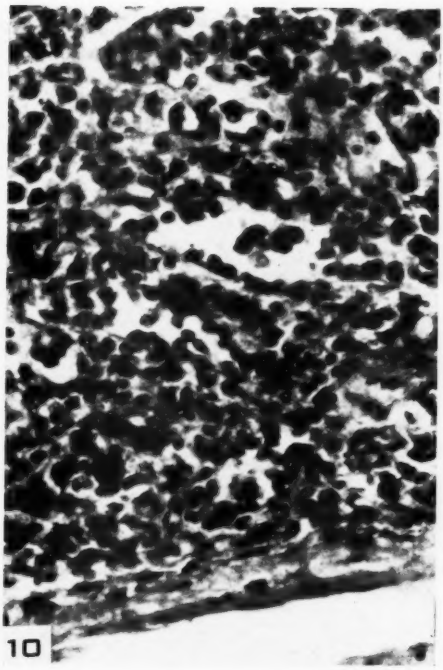
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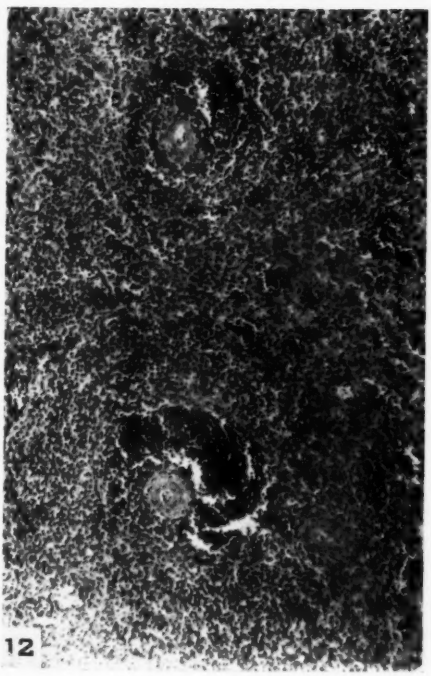
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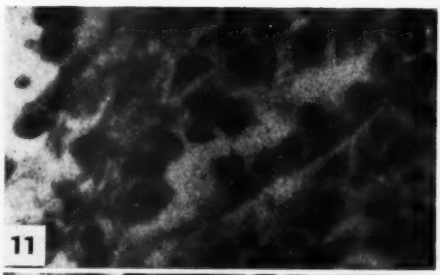
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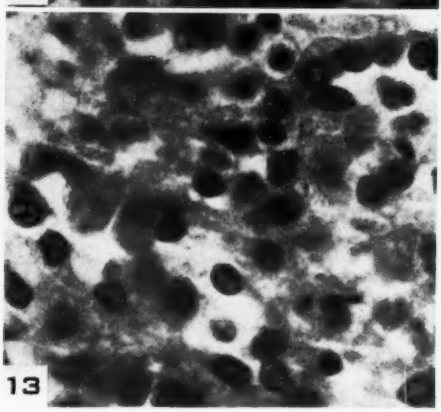
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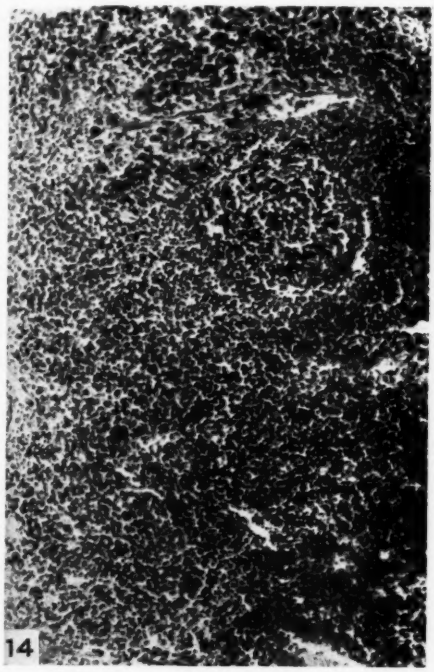
PLATE 30

FIGS 14 and 15. Lymph nodes (cases M.B. and B.K.) with persistent lymphoid follicles separated by masses of plasma cells. × 95.

FIGS. 16 and 17. Lymph nodes (cases R.J. and E.G.) with complete destruction of architecture and invasion of capsule by plasma cells. Other nodes from these same cases were of the type shown in Figures 14 and 15. × 95.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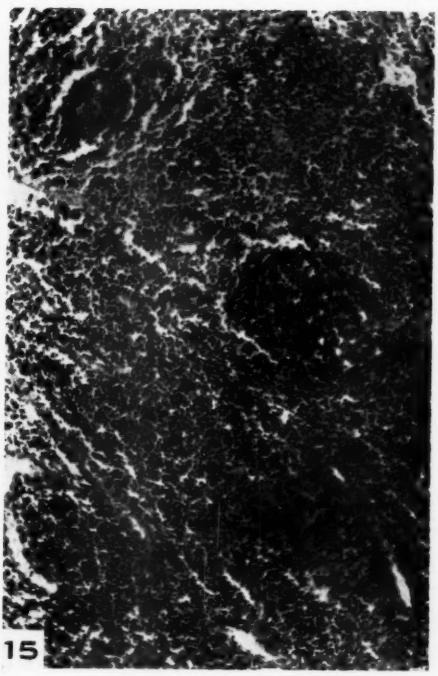
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Lowenhaupt

Proliferative Lesions in Multiple Myeloma

CONGENITAL CYST OF THE MYOCARDIUM *

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An epithelium-lined cyst of the heart is a rare lesion. Such a lesion has interesting theoretical implications as to origin, and so the presentation of an additional case seems warranted.

REPORT OF CASE

The patient, G.F. (A-42-252), was a white male, 44 years old, who had worked as a counterman. He was admitted on July 16, 1942, with severe precordial pain radiating to the left arm and neck for a period of 3 hours. Mild precordial discomfort had been present for the past few days.

On admission, the patient was vomiting. He showed a gray hue to his skin and was sweating. Physical examination revealed nothing of note. The heart sounds were fair, with a regular sinus rhythm of 60. The blood pressure was 110/80 mm. of Hg. The respirations averaged 24 per minute. The urine was negative for albumin and glucose.

In spite of morphine, nembutal, caffeine and sodium benzoate, the patient expired on July 17, 1942, with the final clinical impression of an acute coronary occlusion.

The autopsy confirmed the clinical diagnosis. A fresh thrombus was found in the descending branch of the left coronary artery, approximately 1 cm. below the ostium. Both coronary arteries showed marked atherosclerosis throughout. Microscopically, areas of necrosis and also of old fibrosis were found in the myocardium. The heart weighed 280 gm.

A small cyst situated in the center of the left ventricular wall was an incidental finding (Fig. 1). The cyst measured 0.9 cm. in diameter. Its cavity was rounded and sharply delimited. The lining showed a thin, glossy smooth layer of translucent tissue. The contents of the cyst were gelatinous and translucent, with a pale greenish tint. The cyst was located well within the left ventricular musculature, failing to reach the epicardium or the endocardium. Its lower border was located about 3.5 cm. from the apex. The cyst was completely surrounded by cardiac muscle, and did not occasion any discernible bulging of the muscle toward either the epicardial or the endocardial surface. No external manifestation of its existence was present, and the structure was found only because of a fortunate routine section through its center.

On microscopic examination, an inner layer of epithelial cells was seen. The epithelium was tall columnar for the most part, with a shorter, more cuboidal appearance in some areas. The epithelial lining was distinctly ciliated (Fig. 2). The cilia were numerous, closely placed and of uniform height for each cell. In the shorter cells, the cilia

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were not so tall, but were proportionately more prominent, and, for some cells, occupied as much as one-half the full height of the cell. Most of the cilia of the taller epithelium measured less than one-third or one-fourth the height of the cell structure. The cilia were inserted on a sharp cell border, which appeared as a narrow, linear, condensed eosinophilic zone. The cytoplasm was distinctly granular and eosinophilic. The nuclei were situated in the basilar portions of the cells and were elongated and oval. The nuclei showed some variation in size, but the range of variation in both size and shape was rather narrow.

Discussion and Comparison with Other Cases

Very few similar instances of epithelial cyst formation within the myocardium could be found in the literature. Five of the published cases (Stoeckenius,[1] Kolatschow,[2] Davidsohn,[3] Yamauti [4] and Bayer [5]) represent lesions that are very similar to the one presented here. A sixth case by de Châtel,[6] and two other instances reported by Bayer, differ in many respects. The last three will be discussed separately. There were several features common to the first five cases. They were all situated in the left ventricle of the heart, near or in a papillary muscle. Yamauti and Davidsohn described unilocular formations like the one observed by us, while the cyst reported by Stoeckenius showed subdivisions into several smaller cavities "due to extension between bundles of muscle fibers." Kolatschow described two smaller confluent structures in addition to the oval main cyst. He did not state clearly whether he dealt with one large cystic structure with an irregular invaginating or undulating wall, or with three separate, closely placed cysts. The cysts described by Stoeckenius, Yamauti and Bayer, as well as the lesion presented here, were situated completely within the myocardium. The reports of Kolatschow and Davidsohn note that the cystic structure projected partially into the ventricular cavity.

The ciliated epithelial lining represents an important finding in the five cases with identical features. Its significance lies in the clue it gives to the possible origin of these cystic structures. In the cases of Kolatschow [2] and Davidsohn,[3] as well as in this instance, the contents of the cyst were gelatinous. Yamauti [4] described the contents as homogenous and "pale purple, with hematoxylin-eosin stain." Stoeckenius [1] noted a finely granular meshwork with some clumped desquamated epithelial cells in the contents. Bayer [5] described rounded, albuminoid formations in the lumen. The epithelium is described by Davidsohn as existing in two layers—an outer cuboidal and an inner higher and densely ciliated layer. The cytoplasm in his specimen was eosinophilic

and granular. The nuclei were dark, hyperchromatic and oval, some being highly irregular in shape. Yamauti found "one layer of cuboidal, distinctly ciliated epithelium, with almost oval nuclei, situated in the center of the cells." Kolatschow's case showed columnar ciliated epithelium. He failed to mention the number of layers, but his photomicrograph shows only one distinct layer of epithelial cells. He described the nuclei as "enlarged [ausgedehnten]" possibly meaning elongated, and stated that "they are smaller and more rounded toward the base." Bayer found the cyst lining to consist of one layer of high columnar epithelium with oval, deep-staining nuclei in the lower two-thirds of the cells. Stoeckenius reported columnar cuboidal and flat cells, all showing abundant cilia. Davidsohn, and also Bayer, suggested that the difference in the height of the cells in the last mentioned case may represent an artifact produced by the thickness of the section. The presence of cilia on all of the cells favors this interpretation. The cytoplasm is described by Stoeckenius as "granular, sometimes vacuolated." He described the nuclei as vesicular, elongated or rounded, sometimes hyperchromatic and rod-shaped.

Except for Stoeckenius,[1] all authors mention a thin fibrous wall situated outside of the epithelium. Such a fibrous wall was present in our specimen (Fig. 2). Davidsohn [3] found a distinct homogeneous eosinophilic basement membrane. Bayer [5] found none. A hyaline refractile basement membrane was not made out in hematoxylin and eosin stained sections in our case, but was seen after use of phosphotungstic acid hematoxylin and van Gieson's stains, and best with Verhoeff's elastica stain. No smooth muscle was present, as noted by Bayer. Included atrophic heart muscle fibers were made out, deeply imbedded in the collagenous stroma of the fibrous wall of the cyst.

In none of the reported cases were the cysts found to have clinical significance. In none of them were they diagnosed antemortem. Davidsohn [3] had only negative evidence to support an opinion of a causal relationship for the blowing systolic murmur and thrill which were heard at the base of the heart and then at the apex in his case.

Discussion of Origin

Cystic structures in the heart wall have received different explanations for their origin. All authors agree that the lesion represents a congenital anomaly. According to Stoeckenius,[1] the cyst is due to persistence of the embryologic sponge-like structure of the myocardium, corresponding to the stage of development in fish and amphibians. The cystic structures of this stage are all communicative with the main cavity of the heart, and are lined by endothelium. He assumed that

the endothelium at this stage is multipotent and can differentiate to become columnar and ciliated. The flat cells he observed reminded him of endothelial cells of the epicardium. This theory has the objection that it derives the ciliated columnar epithelium from endothelial cells. As noted above, Davidsohn [3] and Bayer [5] explained the flat cells described by Stoeckenius on the basis of a histologic artifact. This viewpoint would seem to be strengthened, as suggested by Davidsohn, by the fact that all of the cells showed cilia.

Kolatschow [2] presented another hypothesis. He placed the origin from the external part of the myocardial plate, which is the accepted origin for the epicardium, by a process of invagination into the internal plate, which is to become the myocardium proper. This proposal also derives a ciliated columnar epithelium from the mesenchyme. Bayer's [5] case of endothelium-lined cyst and diverticulum may be explained thus. The island of hyaline cartilage found in the wall of this structure may be mesenchymal, though metaplastic origin from epithelium is accepted for this tissue. We have often seen the serous epicardial covering differentiate or undergo metaplasia into rather tall, columnar cells. A cuboidal appearance of the epicardial cells is not at all uncommon. We do not recall, however, any cilia on such an altered epicardial surface layer. Yamauti [4] did not go into details concerning the origin of these cysts. Davidsohn [3] compared the structure with esophageal cysts. He noted a complete absence of embryologic data that would offer an adequate explanation for the cardiac cyst on this basis. Bayer [5] referred the origin of the cystic structure with ciliated epithelium in his case to displaced tissue of the bronchial tree. He pointed out that "as yet no relations between the heart and bronchial tree are found embryologically, but may exist." In favor of the concepts of Davidsohn and Bayer is the fact that, whereas the mesoderm ordinarily fails to produce ciliated epithelium, the entoderm, which is the source of origin for the bronchial tree and esophagus, does do so.

There exists in the early embryo an ideal stage for the heterotopic inclusion of entoderm by the mesoderm which forms the heart. This is seen in the chick embryo when the original flattened germ layers are folded ventrally to establish the body form, the gut lumen and the single heart. The bilateral cardiac Anlagen are in the region of the head at this time, and in intimate contact and partly enclosed by the endoderm to form the foregut. It is during the fusion of the bilateral cardiac primordia to form a single chamber at this juncture that the circumstances seem most favorable for such inclusions. Under this concept, the ciliated cyst of the myocardium represents a *sequestration cyst involving entoderm* in contrast to the mediastinal dermoids, which

may be derived from the ectodermal layer. De Châtel[6] suggested this mechanism of origin for his dermoid cyst.

The entoderm can give origin to squamous epithelium, as in the esophagus, and this heaping up of the epithelial cells occurs early in the embryogenesis of this organ. In some of the lower forms, such as Amphioxus, the esophagus is actually lined by ciliated columnar epithelium. This would mean that the squamous epithelial cysts and the so-called esophageal cysts of the mediastinum can also take origin from the entodermal foregut. It would simplify our problem here if we could assume that the squamous epithelial cysts represent inclusions occurring *later* in the embryonic development of this region. The ciliated cysts represent, then, inclusions occurring very early in the embryo, probably at the time of the formation of the primitive foregut. The case of de Châtel,[6] with both squamous and columnar epithelium in the wall of the same cyst, favors such theoretic considerations. By this concept, the esophageal cysts and the cardiac cysts are closely related, if not identical in origin. No direct factual evidence for any of these theoretic propositions is known to exist in the human embryo.

Conclusion

A cyst of the myocardium, lined by ciliated columnar epithelium, is described, and five similar cases in the literature are reviewed. Consideration of the theoretical implications as to origin results in the suggestion that such cysts arise through the heterotopic inclusion and sequestration of entoderm during the formation of the primitive foregut and single-chambered heart.

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[*Illustrations follow*]

DESCRIPTION OF PLATE

PLATE 31

FIG. 1. Sectioned left ventricular wall, with transected cyst indicated by arrows.

FIG. 2. Photomicrograph of cyst wall showing the ciliated columnar epithelium which lined the cyst, and adjacent stroma. × 400.

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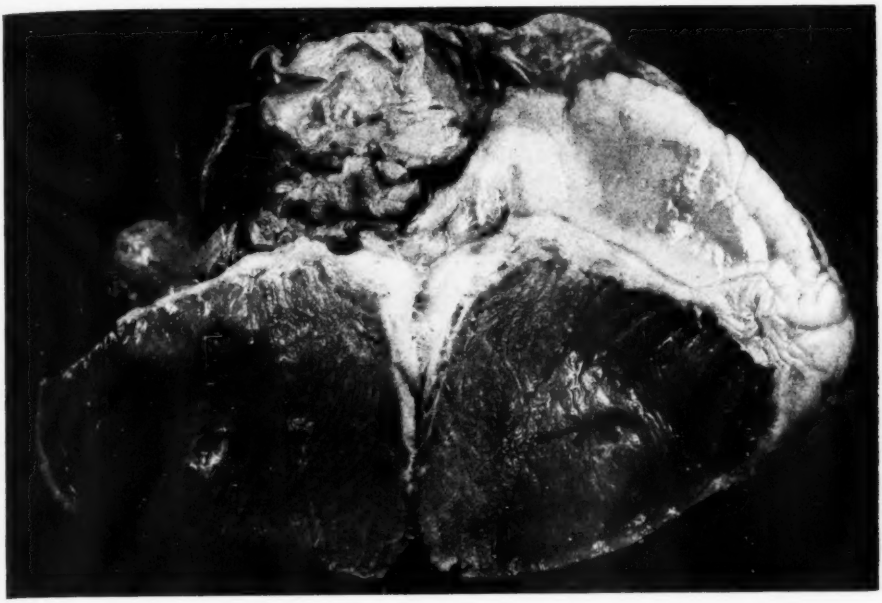

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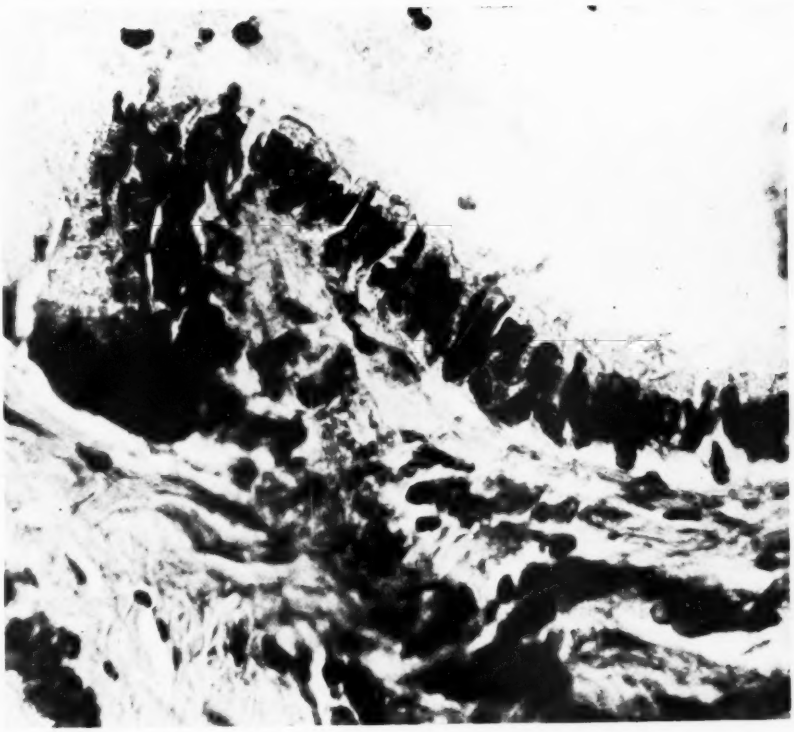

Sachs and Angrist Congenital Cyst of the Myocardium